NHS England

Evidence review: Lung volume reduction using open surgery for severe emphysema

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Contents

1 Introduction

Indication and epidemiology

- Chronic obstructive pulmonary disease (COPD) is a progressive chronic lung disease that is characterised by varying degrees of chronic bronchitis (chronic inflammation of the central airways) and emphysema (van Agteren et al 2016).
- Emphysema is characterised by damaged lung parenchyma with loss of its elasticity, resulting in hyperinflation of the lung, reduced airflow, reduced capacity for efficient gas exchange between the alveoli and the blood, and breathlessness (van Agteren 2016).
- There is no single diagnostic test for COPD, with a diagnosis relying on clinical judgement based on a combination of history, physical examination and confirmation of the presence of airflow obstruction using spirometry (NICE 2010).
- Patients with COPD commonly have increasing breathlessness (particularly a feature of emphysema), a persistent chesty cough with phlegm (chronic bronchitis), frequent chest infections and persistent wheezing, and patients may suffer from weight loss and tiredness. The symptoms usually get gradually worse over time and make daily activities increasingly difficult, although treatment can help slow the progression. For many patients there are periods when symptoms get suddenly worse (exacerbations), particularly during the winter (NHS Choices, 2016).
- According to Public Health England, over one million people in England live with COPD, around 25,000 deaths each year are attributable to COPD, and there were over 113,000 emergency hospital admissions in England due to COPD in 2013/14 (Public Health England, 2015).
- In most cases emphysema results predominantly from cigarette smoke or other noxious particles such as air pollutants, which lead to oxidative stress, chronic inflammation and gradual destruction of lung tissue (van Agteren et al 2016).
- Emphysema can be homogeneous or heterogeneous in the way it affects the lungs. Typically, heterogeneity refers to variation between the lobes of the lungs (interlobar), but it can also be within a lobe (intralobar) (van Agteren et al 2017).
- Conventional treatment for COPD involves short and long-acting bronchodilators, sometimes in combination with inhaled steroids, pulmonary rehabilitation, oxygen supplementation, and a focus on smoking cessation. At more advanced stages of the disease patients respond less well to conventional medical treatment and medical treatment options are limited (van Agteren et al 2017, NICE 2017).

The intervention

- Lung volume reduction surgery (LVRS) is a palliative treatment that aims to remove the most diseased and least functional part of the lungs.
- LVRS aims to improve lung function, quality of life (QoL) and exercise capacity by some combination of:
  i) Increasing pulmonary elastic recoil pressure resulting in increased expiratory airflow,
  ii) Reducing the degree of hyperinflation, resulting in improved mechanics of the diaphragm and chest wall movement, and
  iii) Reducing lung heterogeneity, leading to improved alveolar gas exchange and

increased effectiveness of ventilation (van Agteren et al 2016).

- LVRS reduces the volume of the lung via surgical stapling to cut and seal the tissue, laser ablation to shrink lung volume, or a combination of both. Computed tomography (CT) and perfusion scanning are used to identify the more diseased lung tissue (NICE 2005).
- The two most common techniques used for LVRS are open surgery by median sternotomy (MS) and video-assisted thoracoscopic surgery (VATS). Another surgical approach, thoracotomy, is performed to a lesser extent (van Agteren et al 2016, NICE 2005).
- MS involves cutting through the sternum to open the chest and thoracotomy involves making an incision between the ribs on one side of the chest and separating the ribs to access the lung. VATS is less invasive and involves making a number of small incisions in both sides of the chest to allow the insertion of instruments into the chest between the ribs. (NICE 2005).
- Endobronchial valves are being used increasingly as an alternative to LVRS. This involves placing small one-way valves in some airways leading to damaged parts of the lungs (NICE 2017).
- This review assesses the evidence around LVRS by open surgery (MS or thoracotomy), not VATS.

Existing national policies and guidance

- The National Institute for Health and Care Excellence (NICE) published interventional procedures guidance on lung volume reduction surgery for advanced emphysema (IPG114) in February 2005 (NICE 2005).
- NICE's recommendations are as follows:

"Current evidence on the safety and efficacy of lung volume reduction surgery for advanced emphysema appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance."

"Clinicians wishing to use lung volume reduction surgery for advanced emphysema should ensure that patients are fully informed about the risks of the procedure and the likelihood of deterioration in the longer term. Use of the Institute's information for the public is recommended."

"Patient selection is important because mortality is increased in patients with the most seriously compromised lung function. The Institute has issued a clinical guideline on chronic obstructive pulmonary disease."

"The procedure should be undertaken by a multidisciplinary team that includes a respiratory physician, specialists in pulmonary rehabilitation and a thoracic surgeon."

2 Summary of results

- This evidence review is based on seven papers reporting on one meta-analysis (Miller et al 2005), two RCTs (Naunheim et al 2006, McKenna et al 2004, Fishman et al 2003 (three papers relating to the same RCT) and Hillerdal et al 2005) and two cost-effectiveness analyses (Ramsey et al 2007 and Miller et al 2006) comparing open LVRS to maximal medical management in patients with severe emphysema. No studies were found comparing open LVRS to endobronchial valves.

- The studies all had a prerequisite of pulmonary rehabilitation or physical training programmes prior to enrolment and all continued these programmes for the LVRS patients as well as the control patients as part of their usual medical care.
- The largest study was the National Emphysema Treatment Trial (NETT) which included 1,218 patients and had the longest follow-up with a median of 4.2 years (Naunheim et al 2006). The majority of patients randomised to LVRS had open surgery by MS (70%) with the remainder having VATS. Results for the NET trial are taken from the most recent main NETT paper with longest follow-up (Naunheim et al 2006), except for results on early mortality and complications, which were not reported in that paper, but were reported in earlier NETT papers (Fishman et al 2003 for mortality results and McKenna et al 2004 for complications). Results for early mortality and complication outcomes only, have been taken from these earlier NETT papers (Fishman et al 2003 and McKenna et al 2004), as these outcomes were not reported in the other included studies and it was felt that they are critical to assessing the effectiveness of LVRS.
- The intervention is referred to as open LVRS throughout this RER, although some VATS was carried out by all the studies (maximum of 30% in the LVRS groups).
- The most commonly reported outcomes relate to QoL, exercise capacity, lung function and mortality.

QoL

- The St. George's Respiratory Questionnaire (SGRQ) was used to measure QoL in two studies (Naunheim et al 2006 and Hillerdal et al 2005). Both studies found clinically significant improvements in SGRQ with open LVRS when compared to medical management. Naunheim et al (2016) reported on the percentage of patients with a clinically significant improvement in SGRQ which was defined as a decrease in SGRQ score of greater than eight units over five years. Amongst all patients in the trial (n=1,218), 40%, 32%, 20%, 10%, and 13% of LVRS patients improved in SGRQ by greater than eight points at 1, 2, 3, 4, and 5 years respectively compared to 9%, 8%, 8%, 4%, and 7% of control patients. This represents odds ratios (ORs) of 6.50 ($p<0.001$), 5.27 ($p<0.001$), 3.06 ($p<0.001$), 2.63 ($p=0.05$) and 2.16 ($p=0.12$) at 1, 2, 3, 4, and 5 years respectively. The RCT reported an average initial improvement (time point not defined) of 10.7 units in surviving LVRS patients and a decline of 2.2 units in control patients. Mean values were not reported for other time points. Hillerdal et al (2005) reported a statistically significant mean difference (md) of changes from baseline between the groups of -14.3 (95% CI -19.7 to -9.0) at six months for total SGRQ score. This reduced to -8.8 (95% CI -17.6 to -0.04) at 12 months.
- The Medical Outcomes Study 36-item Short Form (SF-36) was used to measure QoL in two studies (Miller et al 2005 and Hillerdal et al 2005). Both studies found statistically significant mean differences of similar sizes across the SF-36 domains which all showed a greater improvement with LVRS. Miller et al (2005) reported a weighted mean difference (wmd) of 25.94 for physical functioning (95% CI 14.36 to 37.52; $p=0.001$), 14.80 for general health (95% CI 5.62 to 23.98; $p=0.002$), 10.00 for vitality (95% CI 1.30 to 18.71; $p=0.024$) and 6.90 for physical component (95% CI 2.86 to 10.94; $p=0.001$) in favour of LVRS at six months. Hillerdal et al (2005) reported mean differences (of changes from baseline) between the groups of 17.1 (95% CI 9.8 to 24.5) for physical functioning, 20.5 for role physical (95% CI 3.1 to 37.9), 6.8 for general health (95% CI 0.2 to 13.4) and 11.0 for vitality (95% CI 1.3 to 20.6) in favour of LVRS at six months. Further improvements were seen at 12 months, with a mean difference (of changes from baseline) of 19.7 (95% CI 12.1 to 27.3) for physical functioning, 25.2 (95% CI 7.7 to 42.6) for role physical, 9.7 (95% CI 3.2 to 16.2) for general health, 11.4 (95% CI 1.2 to 21.6) for vitality, 21.0 (95% CI 6.2 to

35.7) for social functioning and 13.6 (95% CI 5.2 to 22.0) for mental health.

- The Chronic Respiratory Disease Questionnaire (CRDQ) was used to measure QoL in one study (Miller et al 2005). The study found statistically significant mean differences in all four domains of the CRDQ which included dyspnoea (wmd = 1.56; 95% CI 0.80 to 2.32; p=0.001), fatigue (wmd = 1.17; 95% CI 0.62 to 1.71; p=0.001), mastery (wmd = 1.19 (95% CI 0.63 to 1.74; p= 0.001) and emotion (wmd = 0.87 (95% CI 0.28 to 1.46; p=0.004) in favour of LVRS at six months.

Exercise capacity

- Maximum work was measured by cycle ergometer in two studies (Naunheim et al 2016 and Hillerdal et al 2005). Both studies found evidence to support a greater improvement in maximum work with open LVRS compared to medical management. Naunheim et al (2016) reported on the percentage of patients with a clinically significant improvement in maximum work (defined as increase >10 Watts). Amongst all patients in the trial (n=1,218), 23%, 15%, and 9% of LVRS patients improved in maximum work by >10 Watts at 1, 2 and 3 years respectively compared to 5%, 3%, and 1% of control patients. This represents statistically significant ORs of 5.79 (p<0.001), 5.06 (p<0.001), 7.43 (p<0.001) at 1, 2 and 3 years respectively in favour of LVRS. An average initial improvement (time point not defined) of 5.4 Watts in surviving LVRS patients and a decline by 4.4 Watts in control patients were reported. Mean values were not reported for other time points. Hillerdal et al (2005) reported a mean difference (of changes from baseline) of 11 Watts (95% CI 4 to 18) at six months and 9 Watts (95% CI 0 to 18) at 12 months in favour of LVRS.
- Six-minute walk distance (6MWD) was assessed in one study (Miller et al 2005). The meta-analysis (2005) found a statistically significant mean difference of 148.8 feet 95% CI 24.3 to 273.2; p=0.019) for 6MWD in favour of LVRS at six months, which is a clinically important difference.
- Incremental shuttle walking distance was measured by one study (Hillerdal et al 2005). This RCT found a clinically significant mean difference (of changes from baseline) of 104 metres (95% CI 57 to 151) at six months and 90 metres (95% CI 47 to 133) at 12 months in favour of LVRS.

Lung function

- Many lung function outcomes were reported across the studies. The most commonly used parameter in clinical practice, forced expiratory volume in one second (FEV_1), was reported by two studies and both showed significant improvements with LVRS (Miller et al 2005 and Hillerdal et al 2005).
- Miller et al (2005) reported a significant mean difference of 0.167 litres (95% CI 0.029 to 0.304; p=0.017) for FEV_1 at six months and Hillerdal et al (2005) reported a similar significant mean difference (of changes from baseline) of 0.23 litres (95% CI 0.14 to 0.31) at six months and 0.19 litres (95% CI 0.09 to 0.28) at 12 months.
- Other measures of lung function, including total lung capacity (TLC), residual volume (RV), vital capacity (VC) and partial pressure of carbon dioxide in arterial blood ($PaCO_2$), also showed statistically significant changes that favoured LVRS over medical therapy across the studies. No evidence was found for improvements in diffusion capacity for carbon monoxide (DLCO) between LVRS and medical therapy.

Mortality

- 30-day mortality and 90-day mortality risks were only reported in the NET trial (Fishman et al 2003). Early mortality was found to be significantly higher with LVRS compared to medical management. Among the 1,078 patients who were not at high-risk (high-risk defined as FEV_1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted), the 30-day mortality risk was 2.2% in the LVRS group compared with 0.2% in the control group (p<0.001). The 90-day mortality risk, amongst this group, was 5.2% (95% CI 3.5 to 7.4) in the LVRS group and 1.5% (95% CI 0.6 to 2.9) in the control group (p=0.001).
- Mortality risk in hospital was reported by two studies (Miller et al 2005 and Hillerdal et al 2005). Miller et al (2005) reported that 1/54 (1.85%) of LVRS patients died in hospital after surgery, which is similar to the 30-day mortality rate reported in the NET trial. Hillerdal et al (2005) reported a higher rate of 6/53 (12%).
- Total mortality was reported by all three studies (Naunheim et al 2006, Miller et al 2005 and Hillerdal et al 2005). With the longest follow-up of five years (4.3 years median follow-up), Naunheim et al (2006), found evidence to suggest that despite an increased early mortality with LVRS, in the long-term, overall survival was improved. Amongst all patients in the trial (n=1,218), a total mortality rate of 0.11 deaths per person-year in the LVRS group and 0.13 in the control group was found. This represents a statistically significant improved survival in the LVRS group (overall relative risk (RR) = 0.85; p=0.02).
- The other two studies had shorter follow-up times. Over 12 months, Hillerdal et al (2005) reported that 7/53 (13%) died in the LVRS group (on days 9, 15, 19, 42, 49, 71 & 107 after surgery) mostly due to pneumonia and respiratory failure, compared to 2/53 (4%) in the control group (on days 178 and 215 after randomisation) due to respiratory failure (p=0.489). Over six months, Miller et al (2005) reported that 3/54 (3.6%) patients died in the LVRS group (in hospital, at 4 and 6 months after surgery) compared to 2/39 (5.1%) patients in the control group (within 6 months of randomisation).

Hospital utilisation

- This outcome was reported by one meta-analysis which included two RCTs (Miller et al 2005). Over a six month period, Miller et al (2005) reported that 18/30 (60%) LVRS patients had 27 readmissions in the Canadian Lung Volume Reduction (CLVR) trial and 3/24 (12.5%) LVRS patients had three readmissions in the Overholt-Blue Cross Emphysema Surgery trial (OBEST). In the control groups, 14/28 (50%) of control patients had 38 hospitalisations in the CLVR trial and 1/11 (9%) control patients in the OBEST trial. No confidence intervals or p-values were reported.
- Length of hospital stay after LVRS was also only reported by Miller et al (2005). Over a six-month period, Miller et al (2005) reported that the median length of hospital stay for LVRS was 22 days (range 4 to 161 days) in the CLVR trial and 12 days (range 4 to 57) in OBEST.

Complications

- Data on complications were only reported in the NET trial (McKenna et al 2004). Out of 359 open LVRS patients who were not at high-risk, 7% were reported to have had intraoperative complications which included, amongst others, arrhythmia (1.7%), uncontrolled air leak (0.8%), hypoxaemia (0.8%) and hypercapnia (0.8%).
- Within 30 days after surgery, 58.4% of non-high risk open LVRS patients were reported to have postoperative complications which included, amongst others, arrhythmia (21.3%),

pneumonia (20.1%), tracheostomy (9.2%), failure to wean from ventilation (6.1%), urinary retention (4.2%), failure of early extubation (3.1%), atrial fibrillation (2.5%), reoperation for air leak (2.2%), readmission within 72 hours after discharge (2.2%) and sepsis (2%). Air leak at completion of open LVRS occurred in 54.3% of patients and 46% of patients had air leak for seven or more days.

- Amongst non-high risk open LVRS patients, 43.5% were in the intensive care unit (ICU) for one day or less, 15.3% for two days, 36.2% for 3 to 29 days and 2.3% for 30 days or more. Just over three quarters of patients (76.2%) did not need mechanical ventilation after LVRS.

Sub-group analyses

- Naunheim et al (2016) reported results separately for four predefined subgroups of patients characterised by distribution of emphysema (upper-lobe versus non-upper-lobe predominant) in combination with baseline exercise capacity (high versus low) after excluding patients at high-risk. Low exercise capacity was defined as baseline maximum work of 25 watts or less for women and 40 watts or less for men. Data on mortality and QoL as measured by percentage of patients with an improvement in SGRQ of greater than eight points was available for five years and data on percentage of patients with an improvement in maximum work of greater than 10 Watts was available for three years.
- Amongst patients with upper lobe predominant emphysema and low exercise capacity, (n=290; 24% of trial population), the LVRS group demonstrated lower mortality (overall RR = 0.57; p=0.01) over five years, a greater proportion with improvement in maximum work throughout the three years with data (21% of LVRS patients vs 0% of control patients; p<0.001 at 3 years) and a greater proportion with improvement in QoL throughout the five years of follow-up (19% of LVRS patients vs 0% of control patients; p=0.01 at 5 years).
- Amongst patients with upper lobe predominant emphysema and high exercise capacity (n=419; 34% patients of trial population), the LVRS group demonstrated no significant difference in mortality (overall RR = 0.86; p=0.19), but did show a greater proportion with improvement in maximum work up to three years (10% of LVRS patients vs 2% of control patients; OR = 5.26 (p=0.007) at 3 years) and a greater proportion with improvement in QoL up to four years (17% of LVRS patients vs 4% of control patients; OR = 4.58 (p=0.003) at 4 years).
- Patients with non-upper lobe predominant emphysema and low exercise capacity (n=149; 12% of trial population) demonstrated no significant difference in overall mortality over five years (overall RR = 0.80; p=0.31) and maximum work up to three years (2% of LVRS patients vs 0% of control patients; p>0.99 at 3 years). Initial improvements in QoL were seen in LVRS patients with a greater proportion with improved QoL seen at one year (33% versus 11%, p=0.002) and at two years (27% versus 6%, p=0.002), but this disappeared by three years.
- Patients with non-upper lobe predominant emphysema and high exercise capacity (n=220; 18% of trial population) showed no significant difference in overall mortality over five years (overall RR=1.10; p=0.79) or maximum work over three years (3% versus 4%; p=0.99 at 3 years). Initial improvements in QoL were seen at one year (28% versus 10%; p=0.001) but this disappeared from two years.
- The NETT data monitoring committee (Naunheim et al 2016), excluded patients with FEV1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted as during an interim analysis they were found to be at high risk of dying after LVRS, with a low probability of functional benefit, and were therefore no longer deemed to be eligible for randomisation. Amongst those high-risk patients already randomised (n=140), despite the

initial significantly higher 90-day mortality risk of 28.6% (p<0.001), there was no significant difference in mortality over five years (Overall RR = 1.14; p=0.70). In addition, no significant improvements for exercise capacity or QoL were seen at three years.

Cost-effectiveness

- Ramsey et al (2007) assessed the cost-effectiveness of open LVRS compared to medical management using the long-term NETT data (up to five years) reported in Naunheim et al (2006). Excluding high-risk patients, the cost-effectiveness of LVRS vs medical therapy was found to be $140,000 per QALY gained (95% CI 40,155 to 239,359) at five years and was projected to be $54,000 per QALY gained (confidence intervals not reported) at ten years. The cost-effectiveness of LVRS in patients with upper-lobe predominant emphysema and low exercise capacity (sub-group of patients with greatest benefit) was $77,000 per QALY gained at five years and was projected to be $48,000 per QALY at ten years (confidence intervals not reported).
- The Miller et al (2006) cost effectiveness analysis was based on data from the CLVR trial included in the meta-analysis included in this review (Miller et al 2005). Amongst patients enrolled into the CLVR trial with follow-up data available (n=59), they found a cost per QALY of 133,900 Canadian $ (95% CI 26,000 to undefined) for LVRS compared to medical management.

Summary

- The results are based on one large RCT with long follow-up and two smaller studies with shorter follow-up, all of good quality.
- The evidence suggests that open LVRS is likely to be an effective intervention for improving QoL, exercise capacity and lung function in selected patients with severe emphysema in the short-term with some sustained benefits shown in QoL and exercise capacity in the longer term. Despite the early mortality and complication risks observed with open LVRS, overall long-term survival appears to be improved. Patients with upper lobe emphysema and low exercise capacity were shown to benefit most from open LVRS.
- The cost-effectiveness of open LVRS, even for the sub-group of patients with greatest benefit, is higher than usual commissioning thresholds. Furthermore, the long-term cost-effectiveness estimates are subject to large uncertainty.

3 Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for PICO).
- The PICO was used to search for relevant publications in the following sources: PubMed, Embase, Cochrane, TRIP and NHS Evidence (see section 10 for search strategy).
- The search dates for publications were between 1st January 2002 and 15th January 2018
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were

obtained and reviewed to determine whether they were appropriate for inclusion. Papers which matched the PICO were selected for inclusion in this review, with the exception of non-randomised controlled trials and case series, because sufficient RCT evidence was found.

- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using the National Service Framework for Long-term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).

4 Results

Seven papers are included in this rapid evidence review. These report on one meta-analysis (Miller et al 2005), two RCTs (Naunheim et al 2006, McKenna et al 2004, Fishman et al 2003 (three papers relating to the same RCT) and Hillerdal et al 2005) and two cost-effectiveness analyses (Ramsey et al 2007 & Miller et al 2006) comparing open LVRS to maximal medical management in patients with severe emphysema. No studies were found comparing open LVRS to endobronchial valves.

The largest study was the National Emphysema Treatment Trial (NETT) which included 1,218 patients randomised to LVRS (70% of which had open surgery and the remainder had VATS) or medical management after 6-10 weeks of pulmonary rehabilitation and were followed-up for a median of 4.2 years (Naunheim et al 2006). Results for the NET trial are taken from the most recent main NETT paper with longest follow-up (Naunheim et al 2006), except for results on early mortality and complications, which were not reported in that paper, but were reported in earlier NETT papers (Fishman et al 2003 for mortality results and McKenna et al 2004 for complications). Results for early mortality and complication outcomes only, have been taken from these earlier NETT papers (Fishman et al 2003 and McKenna et al 2004), as these outcomes were not reported in the other included studies and it was felt that they are critical to assessing the effectiveness of LVRS.

The meta-analysis by Miller et al (2005) was not based on a systematic review but pooled the results of two small RCTs (pooled sample size = 93) with similar designs, randomising patients to LVRS or medical management after 6-8 weeks of pulmonary rehabilitation and reporting data at six months. The RCTs were the Canadian Lung Volume Reduction (CLVR) trial which carried out open surgery in all LVRS patients and the Overholt-Blue Cross Emphysema Surgery Trial (OBEST), which carried out open surgery in 75% of the LVRS and the remainder VATS.

The RCT by Hillerdal et al (2005) included 106 patients randomised to LVRS (94% of which had open surgery and the remainder had VATS) or medical management after an intense physical training program for a minimum of six weeks.

Two studies were found comparing the cost-effectiveness of open LVRS to medical management (Ramsey et al 2007 and Miller et al 2006). The cost-effectiveness analysis by Ramsey et al (2007) was based on the long-term NETT data reported in Naunheim et al (2006) and the cost-effectiveness analysis by Miller et al (2006) was based on data from the CLVR trial reported in Miller et al (2005).

Given the RCT evidence found, non-randomised controlled trials and case series were excluded as they provide much lower quality evidence. In addition, systematic reviews and RCTs were excluded where LVRS had been carried out by either open surgery or VATS and the proportion of

open surgery patients was less than 70% or the paper did not report results for open surgery separately.

The intervention is referred to as open LVRS throughout this RER, although some VATS was carried out by all the studies (maximum of 30% in the LVRS groups).

The studies reported on a range of outcomes including mortality, QoL, exercise capacity and lung function. Full details of the study designs and outcomes are summarised in the evidence summary table in section 7.

1) In people with severe emphysema, what is the evidence for the clinical effectiveness and safety for lung volume reduction using open surgery compared to lung volume reduction using endobronchial valves or maximal medical therapy?

a) Do the benefits reach clinically meaningful differences?

QoL – St. George's Respiratory Questionnaire (SGRQ)[1]
This outcome was reported by two studies.

Naunheim et al (2016) reported on the percentage of patients with a clinically significant improvement in SGRQ which is defined as a decrease in SGRQ score of >8 units over five years. Amongst all patients (n=1,218), 40%, 32%, 20%, 10%, and 13% of LVRS patients improved in SGRQ at 1, 2, 3, 4, and 5 years respectively compared to 9%, 8%, 8%, 4%, and 7% control patients. This represents ORs of 6.50 ($p<0.001$), 5.27 ($p<0.001$), 3.06 ($p<0.001$), 2.63 ($p=0.05$) and 2.16 ($p=0.12$) at 1, 2, 3, 4, and 5 years respectively. An average initial improvement (time point not defined) of 10.7 units in surviving LVRS patients and a decline of 2.2 units in control patients was reported. Mean values were not reported for other time points.

Hillerdal et al (2005) reported a significant mean difference (of changes from baseline) between the groups of -14.3 (95% CI -19.7 to -9.0) for total SGRQ score at six months. This reduced to -8.8 (95% CI -17.6 to -0.04) at 12 months. For the symptoms domain, the mean difference was -11.7 (95% CI -20.2 to -3.3) at six months and -17.1 (95% CI -22.7 to -11.6) at 12 months. For the activity domain, the mean difference was -16.8 (95% CI -23.1 to -10.5) at six months and -14.6 (95% CI -20.0 to -9.1) at 12 months. For the impact domain, the mean difference was -13.1 (95% CI -19.2 to -7.0) at six months and -14.7 (95% CI -19.7 to -9.8) at 12 months. All mean differences were statistically significant and in favour of LVRS.

There is evidence to support an improvement in QoL as measured by SGRQ with open LVRS in the short and long-term (up to four years). Minimal clinically important differences (MCID) range from 2 to 8 points in the literature (Jones et al 2014). Naunheim et al (2016) used a greater than 8-point decrease to define a change that is clinically important to patients. Therefore, these results show that LVRS offers clinically meaningful improvements in QoL as measured by the SGRQ for up to four years.

QoL – Medical Outcomes Study 36-item Short Form (SF-36)[2]
This outcome was reported by two studies.

[1] SGRQ is a validated, disease related, self-administered, measure of QoL. It contains 50-items covering symptoms, activities and psychosocial impact.
[2] The SF-36 is a widely used, validated, generic measure of health status which assesses QoL across eight domains, which are both physically and emotionally based. The eight domains are: physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; emotional well-being; social functioning; pain; general health. Scores are presented as a scale from 0 to 100. A high score indicates a more favourable health state.

At six months, Miller et al (2005) reported a weighted mean difference (wmd) of 25.94 for physical functioning (95% CI 14.36 to 37.52; p=0.001), 14.80 for general health (95% CI 5.62 to 23.98; p=0.002), 10.00 for vitality (95% CI 1.30 to 18.71; p=0.024) and 6.90 for physical component (95% CI 2.86 to 10.94; p=0.001) in favour of LVRS. The results for role physical, (wmd = 12.70; 95% CI -7.45 to 32.84; p=0.217), bodily pain (wmd = 2.80; 95% CI -16.43 to 10.82; p=0.687), social functioning (wmd = 8.13; 95% CI -8.35 to 24.62; p=0.334), role emotional (wmd = 10.40; 95% CI -32.31 to 11.52; p=0.352), mental health (wmd = 6.58; 95% CI -0.91 to 14.07; p=0.085) and mental component (wmd = 0.56; 95% CI -6.11 to 4.99; p=0.844) were statistically non-significant.

Hillerdal et al (2005) found similar improvements in SF-36 scores at six months. The RCT reported statistically significant mean differences (of changes from baseline) between the groups for physical functioning (md = 17.1; 95% CI 9.8 to 24.5), role physical (md = 20.5; 95% CI 3.1 to 37.9), general health (md = 6.8; 95% CI 0.2 to 13.4) and vitality (md = 11.0; 95% CI 1.3 to 20.6), all in favour of LVRS.

Further improvements were seen at 12 months, with statistically significant mean differences (of changes from baseline) between the groups of 19.7 (95% CI 12.1 to 27.3) for physical functioning, 25.2 (95% CI 7.7 to 42.6) for role physical, 9.7 (95% CI 3.2 to 16.2) for general health, 11.4 (95% CI 1.2 to 21.6) for vitality, 21.0 (95% CI 6.2 to 35.7) for social functioning and 13.6 (95% CI 5.2 to 22.0) for mental health, all in favour of LVRS.

These results show that LVRS improves QoL in the majority of the domains measured by the SF-36 up to 12 months. No standard MCID has been established for SF-36. One of the included studies in this review defined 5 to be a small change in score and 10 to be a moderate-to-large change in score (Miller et al 2005) so based on this definition, there is evidence to suggest a moderate to large clinically significant effect on QoL with LVRS.

QoL – Chronic Respiratory Disease Questionnaire (CRDQ)[3]
This outcome was reported by one study.

At six months, Miller et al (2005) found statistically significant improvements with LVRS compared to medical management in all four domains of the CRDQ which included dyspnoea (wmd = 1.56; 95 CI 0.80 to 2.32; p=0.001), fatigue (wmd = 1.17; 95 CI 0.62 to 1.71; p=0.001), mastery (wmd = 1.19; 95 CI 0.63 to 1.74; p= 0.001) and emotion (wmd = 0.87; 95 CI 0.28 to 1.46; p=0.004).

The mean differences observed between the two groups across all the CRDQ domains at six months was greater than the widely reported MCID of 0.5 (Goldstein et al 2005). Therefore, there is evidence to support a clinically meaningful improvement in QoL as measured by CRDQ with open LVRS in the short-term.

Exercise capacity – Maximum work, Watts[4]
This outcome was reported by two studies.

Naunheim et al (2016) reported on the percentage of patients with a clinically significant improvement in maximum work (defined as increase in maximum work of >10 Watts). Amongst all patients (n=1,218), 23%, 15%, and 9% of LVRS patients improved in maximum work at 1, 2

[3] CRDQ is a patient reported, disease specific measure of QoL which focuses on four domains: dyspnoea, fatigue, emotional function, and mastery
[4] A measure of integrated cardiopulmonary and physical performance. It is determined by maximal, incremental, symptom-limited exercise using a cycle ergometer. The maximum work load is the highest work level reached (measured in Watts) and maintained for a full minute.

and 3 years respectively compared to 5%, 3%, and 1% of control patients. This represents statistically significant ORs of 5.79 (p<0.001), 5.06 (p<0.001), 7.43 (p<0.001) at 1, 2 and 3 years respectively in favour of LVRS. An average initial improvement (time point not defined) of 5.4 Watts in surviving LVRS patients and a decline by 4.4 Watts in control patients was reported. Mean values for other time points were not reported.

Hillerdal et al (2005) reported a mean difference (of changes from baseline) between the groups of 11 Watts (95% CI 4 to 18) at six months and 9 Watts (95% CI 0 to 18) at 12 months in favour of LVRS.

Naunheim et al (2016) used a greater than 10 Watts increase to define a change that is clinically important to patients. Therefore, there is some evidence to support a clinically important improvement in exercise capacity with open LVRS as measured by cycle ergometer maximum work tests in the medium term (up to three years).

Exercise capacity – Six-minute walk distance (6MWD), feet
This outcome was reported by one study.

Miller et al (2005) reported a statistically significant mean difference between LVRS and medical management group of 148.8 feet (95% CI 24.3 to 273.2; p=0.019) in favour of LVRS at six months.

A 26 metre (85 feet) improvement is most widely considered to be the MCID for 6MWD (Jones et al 2014). Therefore, these results suggest that LVRS offers a clinically meaningful improvement in exercise capacity as measured by the 6MWD for up to six months.

Exercise capacity – Incremental shuttle walking distance (ISWD), metres[5]
This outcome was reported by one study.

Hillerdal et al (2005) found a statistically significant mean difference (of changes from baseline) between the groups of 104 metres (95% CI 57 to 151) at six months and 90 metres (95% CI 47 to 133) at 12 months in favour of LVRS.

An MCID for ISWD is considered to be 47.5 metres (Jones et al 2014). Therefore, these results suggest that LVRS offers a clinically meaningful improvement in exercise capacity as measured by the ISWD up to 12 months.

Lung function – Forced expiratory volume in one second (FEV_1), litres
This outcome was reported by two studies.

Miller et al (2005) reported a significant mean difference of 0.167 litres (95% CI 0.029 to 0.304; p=0.017) for FEV_1 in favour of LVRS at six months.

Hillerdal et al (2005) reported a statistically significant mean difference (of changes from baseline) between the groups of 0.23 litres (95% CI 0.14 to 0.31) for FEV_1 at six months and 0.19 litres (95% CI 0.09 to 0.28) at 12 months in favour of LVRS.

An increase of 0.1 litres is widely considered to be an MCID (Jones et al 2014). Therefore, these results show that LVRS offers a clinically meaningful improvement in lung function as measured by FEV_1 up to 12 months.

[5] The incremental shuttle walking distance (ISWD) is a progressive exercise test where patients walk 10 metres at a set speed. After each 10 metres, the speed is increased in a standardised manner until point of intolerance. It measures total distance walked.

Lung function – Total lung capacity (TLC), litres
This outcome was reported by two studies.

Miller et al (2005) reported a significant mean difference of -1.044 litres (95% CI -1.483 to -0.605; p<0.001) for TLC in favour of LVRS at six months.

Hillerdal et al (2005), reported a lower mean difference (of changes from baseline) of -0.36 litres (95% CI -0.80 to -0.08) at six months and -0.48 litres (95%CI -0.91 to -0.05) at 12 months in favour of LVRS.

These results show that open LVRS results in a reduction in TLC in patients with severe emphysema. However, no MCID could be found in the literature so it is not clear if these changes are important clinically.

Lung function – Residual volume, litres
This outcome was reported by two studies.

Miller et al (2005) reported a significant mean difference of -0.1342 litres (95% CI -0.1844 to -0.0840; p<0.001) for RV in favour of LVRS at six months.

Hillerdal et al (2005) reported a non-significant mean difference (of changes from baseline) between the groups of -0.94 litres (95% CI -1.37 to 0.52) at six months and a significant mean difference of -1.00 litres (95% CI -1.37 to -0.62) at 12 months in favour of LVRS.

These results provide evidence of a reduction in RV with open LVRS at 12 months but the results at six months are uncertain. Reductions of 350 ml and 430 ml have been defined in studies as MCIDs (van Agteren et al 2017) which would mean that the 12-month reduction of 1 litre would be clinically meaningful to patients.

Lung function – Vital capacity (VC), litres
This outcome was reported by one study.

Hillerdal et al (2005) reported a significant mean difference (of changes from baseline) of 0.45 litres (95% CI 0.18 to 0.72) for VC at six months and 0.39 litres (95% CI 0.13 to 0.65) at 12 months in favour of LVRS.

There is evidence of a reduction in VC with open LVRS in the short term. However, no MCID was found in the literature so it is not clear whether this is of clinical importance.

Lung function – diffusion capacity of the lung for carbon monoxide (DLCO), mL/min/mm Hg
This outcome was reported by one study.

Miller et al (2005) reported a non-significant mean difference for DLCO of 0.9810 mL/min/mm Hg (95% CI -0.334 to 2.296; p=0.144) at six months.

There is no evidence to support an improvement in DLCO with open LVRS.

Lung function – Partial pressure of carbon dioxide in arterial blood ($PaCO_2$), mm Hg
This outcome was reported by one study.

Miller et al (2005) reported a significant mean difference for $PaCO_2$ of -3.7183 mm Hg (95% CI -6.960 to -0.477; p=0.025) in favour of LVRS at six months.

There is evidence to support a reduction in $PaCO_2$ with open LVRS in the short term. However, no MCID was found in the literature so it is not clear whether the size of the reduction is meaningful clinically.

Mortality – 30-day mortality, %
This outcome was reported by one study.

In an earlier analysis of the NET trial, Fishman et al (2003) reported that among the 1,078 patients who were not at high-risk (excluding those with FEV_1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted), the 30-day mortality risk was 2.2% in the LVRS group compared with 0.2% in the control group (p<0.001). Results were not reported for all patients including those of high risk.

There is evidence to suggest an increased risk of mortality within 30 days after open LVRS compared to usual medical care.

Mortality – 90-day mortality, %
This outcome was reported by one study.

In an earlier analysis of the NET trial, Fishman et al (2003) reported a 90-day mortality risk amongst all patients of 7.9% (95% CI 5.9 to 10.3) in the LVRS group and 1.3% (95% CI 0.6 to 2.60) in the control group. This represents a statistically significant higher risk with LVRS (p<0.001). Amongst non-high-risk patients, the risk was 5.2% (95% CI 3.5 to 7.4) in the LVRS group and 1.5% (95% CI 0.6 to 2.9) in the control group (p=0.001), and amongst high-risk patients it was 28.6% (95% CI 18.4 to 40.6) in LVRS group and 0% (95% CI 0 to 5.1) in control group.
There is evidence to suggest an increased risk of mortality within 90-days after open LVRS compared to usual medical care.

Mortality – In hospital mortality, %
This outcome was reported by two studies.

Miller et al (2005) reported that 1/54 (1.85%) of LVRS patients died in hospital after surgery, which is similar to the 30-day mortality rate reported in the NET trial.

Hillerdal et al (2005) reported a higher rate of 6/53 (12%) caused by pneumonia and respiratory failure (on days 9, 15, 19, 42, 49, and 71).

No results were reported for the control group for the same time period so it is not known whether these are significantly different to the mortality rate in control patients for the same time period.

Mortality – Total mortality, deaths per person-year
This outcome was reported by all three studies.

Over five years (4.3 years median follow-up), Naunheim et al (2006) reported a total mortality rate of 0.11 deaths per person-year in the LVRS group and 0.13 in the control group for all patients in the trial. This represents a statistically significant lower risk of death in the LVRS group (overall RR = 0.85; p=0.02). Excluding those of high-risk (n=1078), the total mortality rate was 0.10 deaths per person-year in the LVRS group and 0.12 deaths per person-year in the control group (Overall RR = 0.82; p=0.02). Among high-risk patients only (n=140), the overall relative risk was

1.14 (p=0.70).

Over 12 months, Hillerdal et al (2005) reported that 7/53 (13%) died in the LVRS group (on days 9, 15, 19, 42, 49, 71 & 107 after surgery) mostly due to pneumonia and respiratory failure, compared to 2/53 (4%) in the control group (on days 178 and 215 after randomisation) due to respiratory failure. This represents a non-significant difference (p=0.489).

Over six months, Miller et al (2005) reported that 3/54 (3.6%) patients died in the LVRS group (in hospital, at 4 and 6 months after surgery) compared to 2/39 (5.1%) patients in the control group (within 6 months of randomisation). No confidence intervals or p-values are reported but this is likely to represent a non-significant difference.

There is evidence to suggest that despite a likely increased early mortality with LVRS, in the long-term, overall survival is improved in open LVRS compared to usual medical care.

Complications - Intraoperative complications, %
This outcome was reported by one study (McKenna et al 2004).

Out of 359 open LVRS patients who were not at high-risk[6], 7% were reported to have had intraoperative complications which included arrhythmia (1.7%), uncontrolled air leak (0.8%), hypoxaemia (0.8%), hypercapnia (0.8%), hypotension (0.3%), cardiac arrest (0.3%), and other complications (3.3%). Only percentages were reported, not number of patients.

The mean blood loss during open LVRS was 138.0 ml and 3.1% of patients needed a transfusion.

Complications - Postoperative complications, %
This outcome was reported by one study (McKenna et al 2004).

Out of 359 open LVRS patients who were not at high risk, 58.4% of open LVRS patients were reported to have postoperative complications within 30 days after surgery which included arrhythmia (21.3%), pneumonia (20.1%), tracheostomy (9.2%), failure to wean from ventilation (6.1%), urinary retention (4.2%), failure of early extubation (3.1%), atrial fibrillation (2.5%), reoperation for air leak (2.2%), readmission within 72 hours after discharge (2.2%), sepsis (2%), epidural catheter complications (1.1%), mediastinitis (0.8%), sternal debridement (0.8%) and pulmonary embolus (0.6%).

Out of 359 open LVRS patients who were not at high risk, air leak at completion of open LVRS occurred in 54.3% of patients. Out of those patients with data on air leak after completion (n=339), 46% of patients had air leak for seven or more days.

Out of 354 open LVRS patients who were not at high risk, 43.5% were in the intensive care unit (ICU) for one day or less, 15.3% for two days, 36.2% for 3 to 29 days, 2.3% for 30 days or more and 2.8% were dead within 30 days of LVRS. The reason for not including the full 359 patients is not reported.

Out of 357 open LVRS patients who were not at high risk, 76.2% did not need mechanical ventilation after LVRS, 6.4% required one day, 6.2% for 2-14 days, 7.6% for 15-29 days, 0.8% for 30 days or more and 2.8% were dead within 30 days of LVRS. Only percentages were reported. The reason for not including the full 359 patients is not reported.

Only percentages were reported, not number of patients having complications. When calculating

[6] High risk defined as patients with FEV1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted.

the percentages, it appears that data for patients who died within 30 days of surgery were excluded from the numerator for each duration of complication for air leak, ICU stay and mechanical ventilation but were included in the denominator.

Percentage hospitalised, living in a nursing or rehabilitation facility (or unavailable for interview but not known to be dead)
This outcome was reported by one study.

Naunheim et al (2006) reported that 28.1%, 14.3%, 6.7%, and 3.3% of LVRS patients were hospitalised, living in a nursing or rehabilitation facility (or unavailable for interview but not known to be dead) at 1, 2, 4 and 8 months, respectively compared to 2.2%, 3.3%, 3.2% and 3.7% of control patients. These represented statistically significant differences between the groups at 1 to 4 months, but not at 8 months where only a 0.4% difference was observed in the group.

There is evidence to suggest that patients are more likely to be hospitalised or living in a nursing or rehabilitation facility up to four months after surgery, but no significant difference was seen more long-term at eight months between LVRS and medical management.

Hospital admissions
This outcome was reported by one study.

Over a six-month period, Miller et al (2005) reported that 18/30 (60%) LVRS patients had 27 readmissions in the CLVR trial and 3/24 (12.5%) LVRS patients had three readmissions in the OBEST trial. In the control groups, 14/28 (50%) of control patients had 38 hospitalisations in the CLVR trial and 1/11 (9%) control patients in the OBEST trial. No confidence intervals or p-values were reported so it is not clear whether there was a significant difference in hospital admissions between the groups.

Length of hospital stay
This outcome was reported by one study.

Over a six-month period, Miller et al (2005) reported that the median length of hospital stay for LVRS was 22 days (range, 4 to 161 days) in the CLVR trial and 12 days (range, 4 to 57) in the OBEST trial.

b) Are there any subgroups of patients who are likely to derive the greatest benefit from the intervention(s)?
Naunheim et al (2016) reported results separately for four predefined subgroups of patients characterised by distribution of emphysema (upper-lobe versus non-upper-lobe dominant) in combination with baseline exercise capacity (high versus low). Low exercise capacity was defined as baseline maximum work of 25 watts or less for women and 40 watts or less for men. Data on mortality and QoL as measured by percentage of patients with an improvement in SGRQ of greater than 8 points was available for five years and data on percentage of patients with an improvement in maximum work of greater than 10 Watts was available for three years.

After excluding high-risk patients[7], LVRS patients with upper lobe predominant disease demonstrated significant advantages over the control group in maximum work and QoL, and for patients who also had low exercise capacity at baseline, improved survival.

Amongst patients with upper lobe predominant emphysema and low exercise capacity, (n=290; 24% of trial population), the LVRS group demonstrated lower mortality compared to controls

[7] High risk defined as patients with FEV1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted.

(overall RR = 0.57; p=0.01) over five years, a greater proportion with improvement in maximum work (defined as increase in maximum work of >10 Watts) throughout the three years with data (21% of LVRS patients vs 0% of control patients; p<0.001 at 3 years) and a greater proportion with improvement in QoL (defined as decrease in SGRQ score of >8 units) throughout the five years of follow-up (19% of LVRS patients vs 0% of control patients; p=0.01 at 5 years).

Amongst patients with upper lobe predominant emphysema and high exercise capacity (n=419; 34% patients of trial population), the LVRS group demonstrated no significant difference in mortality compared to controls (overall RR = 0.86; p=0.19) over five years, but did show a greater proportion with improvement in maximum work up to three years (10% of LVRS patients vs 2% of control patients; OR = 5.26 (p=0.007) at 3 years) and a greater proportion with improvement in QoL up to four years (17% of LVRS patients vs 4% of control patients; OR = 4.58 (p=0.003) at 4 years). These improvements were smaller than those observed for upper lobe dominant with low exercise capacity patients.

Data was not found on differences between heterogeneous and homogenous emphysema patients, and those with and without collateral ventilation.

c) Are there any condition and intervention specific exclusions that reduce the patients' ability to benefit or that reduce the duration of that benefit.

The NETT data monitoring committee (Naunheim et al 2016), excluded patients with FEV1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted as during an interim analysis they were found to be at high risk of dying after LVRS, with a low probability of functional benefit, and were therefore no longer deemed to be eligible for randomisation.

Amongst those high-risk patients already randomised (n=140), there was no significant difference in mortality over five years (overall RR = 1.14; p=0.70) for open LVRS compared to medical management. However, they had a significantly higher 90-day mortality risk of 28.6% (95 % CI 18.4 to 40.6) for LVRS compared to 0% (95 % 0 to 5.1) for medical management (p<0.001).

Amongst the high-risk patients only (n=140), statistically significant improvements in QoL were seen with LVRS compared to medical management for up to two years, with 20%, 11%, 6%, 0%, and 0% of LVRS patients improving in SGRQ (> 8 points) at 1, 2, 3, 4, and 5 years, respectively compared to 4%, 1%, 3%, 0%, and 0% of control patients. This represents ORs of 5.58 (p=0.01), 8.90 (p=0.03), 1.78 (p=0.69) at 1, 2 and 3 years respectively. Mean values not reported.

Amongst high-risk patients only (n=140), statistically significant improvements in maximum work were seen for LVRS compared to medical management up to one year, with 11%, 7%, and 2% of LVRS patients improving at 1, 2 and 3 years, respectively compared to 1%, 3%, and 2% of control patients. This represents ORs of 8.90 (p=0.03), 2.62 (p=0.44) and 0.83 (p>0.99) at 1, 2 and 3 years respectively. Mean values were not reported.

In the NET trial (Naunheim et al 2016), after excluding high-risk patients, patients with non-upper lobe predominant emphysema demonstrated no significant differences in survival and exercise capacity and any little chance of symptomatic improvement, disappeared by three years.

Specifically, patients with non-upper lobe predominant emphysema and low exercise capacity (n=149; 12% of trial population) demonstrated no significant difference in overall mortality over five years (overall RR = 0.80; p=0.31) and maximum work over three years (2% of LVRS patients vs 0% of control patients; p>0.99 at 3 years). Although LVRS patients had a greater proportion with improved QoL at one year (33% versus 11%, p=0.002) and at two years (27% versus 6%,

p=0.002), this disappeared by three years. Patients with non-upper lobe predominant emphysema and high exercise capacity (n=220; 18% of trial population) showed no significant difference in overall mortality over five years (overall RR=1.10; p=0.79) or maximum work over three years (3% versus 4%; p=0.99 at 3 years). Initial improvements in QoL were seen at one year (28% versus 10%; p=0.001) but this disappeared from two years.

Hillerdal et al (2005) reported that age, sex, and baseline characteristics, including differences in α1-antitrypsin levels, were not related to improvements seen in QoL (measured by SGRQ) with LVRS.

2) Is there any evidence of cost effectiveness of LVRS using open surgery compared to maximal medical support?
Two studies were found comparing the cost-effectiveness of open LVRS to medical management (Ramsey et al 2007 & Miller et al 2006).

Ramsey et al (2007) cost-effectiveness analysis was based on the long-term NETT data reported in Naunheim et al (2006) and estimated at ten years using modelling based on observed trends in survival, cost, and QoL. This cost-effectiveness analysis is an update on the NETT cost-effectiveness analysis reported in 2003 (Ramsey et al 2003).

Amongst non-high-risk patients with severe emphysema and Medicare data available (n=1,066), the cost-effectiveness of LVRS vs medical therapy was found to be $140,000 per QALY gained (95% CI 40,155 to 239,359) at five years and was projected to be $54,000 per QALY gained (confidence intervals not reported) at ten years. The cost-effectiveness of LVRS in patients with upper-lobe predominant emphysema and low exercise capacity (patient sub-group with greatest benefits) was $77,000 per QALY gained at five years and was projected to be $48,000 per QALY at ten years (confidence intervals not reported) (Ramsey et al 2007). Costs were from a US setting and included medical goods and services, transportation to and from health-care facilities, time spent by family and friends caring for the patient, and time spent in treatment. Costs were estimated using Medicare claims and clinical trial reporting forms.

Miller et al (2006) cost effectiveness analysis was based on data from the CLVR trial included in the meta-analysis included in this review (Miller et al 2005). Amongst patients with severe emphysema (n=59), they found a cost per QALY of 133,900 Canadian $ (95% CI 26,000 to undefined) for LVRS compared to medical management. Costs were from a Canadian setting and included surgery, hospital stay, intensive care unit stay, GP visits, ER visits, specialist visits, oxygen use and rehabilitation.

3) What is the cost-effectiveness of LVRS using open surgery compared to lung volume reduction by endobronchial valves?
No studies were found comparing open LVRS to endobronchial valves.

5 Discussion

Three studies were found comparing open LVRS to medical management in patients with severe emphysema. These included one meta-analysis (Miller et al 2005) of two RCTs, and two RCTs (Naunheim et al 2006, McKenna et al 2004, Fishman et al 2003 (three papers relating to the same RCT) and Hillerdal et al 2005). In addition, two cost-effectiveness analyses were found (Ramsey et al 2007 and Miller et al 2006).

The studies recruited highly selected patient populations generally based on lung function values and emphysema pattern shown on a CT scan. Out of those considered initially suitable for LVRS by the trials, only 12%-38% of patients met the eligibility criteria and were included. In addition, two of the included studies (Naunheim et al 2006 and Hillerdal et al 2005), excluded high-risk patients partway through the trial as the data monitoring committee deemed them to be of high risk of mortality with little functional gain. The majority of patients in Miller et al (2005) and all patients in Hillerdal et al (2005) had heterogeneous emphysema, whereas Naunheim et al (2006) included patients with both heterogeneous (55% of patients) and homogenous emphysema. These strict eligibility criteria limit the applicability of the results and show that careful screening of patients is needed prior to surgery.

The studies all had a prerequisite of around six weeks of pulmonary rehabilitation or physical training programmes prior to enrolment. All of the studies continued these programmes in addition to medical therapy for the intervention patients as well as the control patients for the duration of the study. Hillerdal et al (2005) differed slightly and included a physical training programme, consisting of small group sessions with bicycle ergometer and muscle strength exercises and a home exercise programme, for three months for the intervention group and one year for the control group.

None of the studies had an intervention group consisting of only open LVRS. The proportion of MS ranged from 70% (Naunheim et al 2006) to 94% (Hillerdal et al 2005).

The largest study by far was the National Emphysema Treatment Trial (NETT) which included 1,218 patients and had the longest follow-up with a median of 4.2 years (Naunheim et al 2006, McKenna et al 2004, Fishman et al 2003). Results for the NET trial are taken from the most recent main NETT paper with longest follow-up (Naunheim et al 2006). However, as this paper did not report on early mortality and complications, two earlier NETT papers were also included in the RER (Fishman et al 2003 for mortality results and McKenna et al 2004 for complications). Results for early mortality and complication outcomes only, have been taken from these earlier NETT papers as these outcomes were not reported in the other included studies and it was felt that they are critical to assessing the effectiveness of LVRS.

The other two studies had relatively small sample sizes of around 100 patients and follow-up times up to one year. The meta-analysis (Miller et al 2005) was not based on a systematic review and only included two small RCTS (CLVR and OBEST trials) of similar design with data at six months. One of the trials included (CLVR) included a cost-effectiveness analysis and the results of this have been included in this review.

All of the studies were generally well-conducted, with few limitations. One issue common to all, was that patients were not blinded to allocation as none of the trials included a sham procedure for control patients. Although it would be unethical to include a sham procedure, it should be noted that the lack of blinding could introduce performance bias and a placebo effect in favour of open LVRS, particularly for the subjective QoL outcomes and motivational dependent exercise capacity outcomes, thus exaggerating the apparent effectiveness of the intervention. Miller et al (2005) reported that outcome assessors were blinded, but in practice this would have been difficult to achieve as patients could disclose their allocation. Also some of the LVRS patients would have been recovering in hospital or were discharged with clear signs of surgery. However, this is unlikely to introduce significant detection bias as the outcomes assessed by the research assistants were mostly objective.

All studies performed intention-to-treat analyses, which is important as there was some cross-over

in both directions. For example, in the NET trial, in the LVRS group, 3.5% refused surgery, and 1.2% were judged unsuitable for surgery after randomisation, and in the control group, 7.2% were known to have received LVRS outside of NETT, and 3.1% received lung transplants during follow-up (Naunheim et al 2006). One other issue to note, is that the long-term results in NETT are based on smaller numbers with only around three quarters of patients participating in the extension of follow-up.

Naunheim et al (2006) mostly reported outcomes for QoL, exercise capacity and lung function as dichotomised endpoints, not average values, reporting on the percentage of patients reaching clinically meaningful improvements. This meant that it was not always possible to determine the exact size of effect.

A further issue is that all of the studies started recruitment over 20 years ago and it is likely that patient selection for LVRS, surgery procedures and medical management have improved since then affecting the applicability of these results to today's patients.

Despite these limitations, the evidence appears to suggest that open LVRS is likely to offer clinically meaningful improvements in QoL, exercise capacity and lung function for select patients with severe emphysema in the short-term with some sustained functional benefits in the longer term.

The surgery is not without risk with higher rates of early mortality observed across the studies. The NET trial reported a 30-day mortality risk (excluding high-risk patients) of 2.2% in the LVRS group compared with 0.2% in the control group ($p<0.001$) and a 90-day mortality risk of 5.2% (95% CI 3.5 to 7.4) in the LVRS group and 1.5% (95% CI 0.6 to 2.9) in the control group ($p=0.001$) (Fishman et al 2003). The other studies reported higher in-hospital mortality rates, but they were unlikely to reach statistical significance due to the small sizes involved.

However, despite this increased early mortality with LVRS, the extended follow-up of NETT has shown that in the longer-term, overall survival is improved (Naunheim et al 2006). Amongst all patients, the RCT found a total mortality rate of 0.11 deaths per person-year in the LVRS group and 0.13 in the control group over five years.. This represents a statistically significant improved survival in the LVRS group (overall RR = 0.85; $p=0.02$).

This longer-term survival benefit appears to be greatest in patients with upper lobe predominant emphysema and low exercise capacity at baseline (RR = 0.57; $p=0.01$; Naunheim et al 2006). This group of patients also showed the greatest improvements in exercise capacity and QoL. Patients with upper lobe predominant emphysema and high exercise capacity at baseline also showed improvements in exercise capacity and QoL, but to a lesser extent and they showed no significant survival improvement (overall RR = 0.86; $p=0.19$) over five years. Patients with non-upper lobe predominant emphysema demonstrated no significant differences in survival and exercise capacity and any little improvement in QoL, disappeared by three years. Data was not found on differences between heterogeneous and homogenous emphysema patients, and those with and without collateral ventilation.

Only McKenna et al 2004 reported on complications associated with open LVRS in an earlier NETT paper comparing the safety and effectiveness of open surgery to video assisted thoracoscopic surgery (VATS) in the non-high-risk patients. The results for the open surgery LVRS patients only (n=359), suggest a moderate complication rate during open LVRS of 7% and a high rate of complications in the 30 days after open LVRS with 58.4% of patients having a postoperative complication. Air leak was found to be particularly high with just over a half of patients (54%) having air leak on completion of LVRS, followed by arrhythmia (21.3%) and

pneumonia (20.1%).

Although LVRS appears to offer clinically meaningful benefits and improved survival in some patients, the procedure is relatively costly and does not appear to be cost-effective even amongst patients with the greatest benefit. Two cost-effectiveness analyses were found comparing LVRS to medical management in severe emphysema (Ramsey et al 2007 and Miller et al 2006). Ramsey et al 2007 estimates were based on the long-term NETT data and hence offered the most robust estimates. Excluding high-risk patients, they found the cost-effectiveness of LVRS vs medical therapy to be $140,000 per QALY gained (95% CI 40,155 to 239,359) at five years and $54,000 per QALY gained (confidence intervals not reported) at ten years. The cost-effectiveness of LVRS in patients with upper-lobe emphysema and low exercise capacity at baseline (sub-group of patients with greatest benefit) was $77,000 per QALY gained at five years and was projected to be $48,000 per QALY at ten years (confidence intervals not reported). Large uncertainty remains around the 10-year cost per QALYs as they are based on estimates of survival and QoL. In addition, the sub-group results and latter follow-up time points are based on small numbers so will also have wide confidence intervals. A further limitation is that the costs are from a US perspective and are over ten years old so may not be applicable to the UK. Furthermore, the costs included medical goods and services, time spent in treatment, transportation to and from health-care facilities and time spent by family and friends caring for the patient, and some of these would not usually be included in cost-effectiveness studies carried out for the UK NHS.
No studies were found comparing open LVRS to endobronchial valves.

6 Conclusion

The evidence surrounding open LVRS compared to medical management is dominated by one well-conducted, large RCT with relatively long follow-up.

The evidence suggests that open LVRS is likely to be an effective intervention for improving QoL, exercise capacity and lung function in select patients with severe emphysema in the short-term with some sustained benefits shown in QoL and exercise capacity in the longer term. Despite the early mortality and complication risks observed with open LVRS, overall long-term survival appears to be improved. Patients with upper lobe predominant emphysema and low exercise capacity were shown to benefit most from open LVRS.

The cost-effectiveness of open LVRS, even for the sub-group of patients with greatest benefit, appears to be low. Furthermore, the cost-effectiveness estimates are based on North American healthcare systems and may not be applicable to the UK NHS.

No studies were found comparing open LVRS to endobronchial valves.

7 Evidence Summary Table

For abbreviations see list after each table

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Miller et al (2005) Canada & USA	S1 Meta-analysis of existing data analysis Combines the data of 2 RCTs - Canadian Lung Volume Reduction (CLVR) trial & the Overholt-Blue Cross Emphysema Surgery Trial (OBEST) Recruitment = 1997-2002 6-month f/up	n = 93 (CLVR = 58 & OBEST = 35) Patients with severe emphysema, marked airflow limitation (i.e., FEV_1, 15 to 40% predicted), hyperinflation TLC > 120% predicted), $PaCO_2$ < 55 mm Hg, and measurable dyspnoea. Baseline (BL) characteristics: Age years, mean (SD) = 63.86 (6.65) Males = 55 (59%) BMI kg/m^2, mean (SD) = 23.79 (3.92) Smoking pack-years, mean (SD) = 59.40 (27.89)	n = 54 LVRS MS in 30/30 (100%) for CLVR & 18/24 (75%) for OBEST Plus usual medical care including pulmonary rehabilitation. n = 39 control Usual medical (medical therapy & pulmonary rehabilitation)	Primary Clinical effectiveness	Six-minute walk distance (6MWD), feet	At BL (mean, SD): LVRS (n=54) = 1,077 (337) Control (n=39) = 1,102 (299) At 6 months (mean, SD): LVRS (47) = 1,223 (331) Control (34) = 1,041 (348) weighted mean difference (wmd) = 148.8 (95% CI 24.3 to 273.2; p=0.019) in favour of LVRS	8	Direct	Before randomisation, eligible patients completed 6 to 8 weeks of pulmonary rehabilitation. Randomisation methods of the 2 RCTs are clearly described and appear adequate. Attempted to keep outcome assessors blind to allocation, but not achieved in all cases. Three patients did not undergo LVRS (one withdrew, one refused surgery & one had a lung malignancy). Five patients died during the follow-up period and did not complete follow-up. 79.5% of patients had pulmonary function test results, 85.2% had CRDQ scores, 85.2% SF-36 and 90.9% 6MWD results. Intention-to-treat analysis (ITT) analysis carried out. A meta-analysis of two RCTs with similar design. Not a
					Quality of life (QoL) measured by the Chronic Respiratory Disease Questionnaire (CRDQ)[8]	Means at BL & 6 months for each group not reported. wmd at 6 months: Overall CRDQ score not reported Dyspnoea = 1.56 (95% CI 0.80 to 2.32; p=0.001) Fatigue = 1.17 (95% CI 0.62 to 1.71; p=0.001) Mastery = 1.19 (95% CI 0.63 to 1.74; p= 0.001) Emotion = 0.87 (95% CI 0.28 to 1.46; p=0.004) All in favour of LVRS.			
				Secondary Clinical effectiveness	QoL measured by the Medical Outcomes Study 36-item	Means at BL & 6 months for each group not reported. wmd at 6 months: Overall SF-36 score not reported.			

[8] CRDQ is a patient reported, disease specific measure of QoL which focuses on four domains: dyspnoea, fatigue, emotional function, and mastery

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		FEV_1 mL, mean (SD) = 689 (23.6) RV mL, mean (SD) = 5,431 (255) TLC L, mean (SD) = 7.87 (1.51) DLCO mL/min/mm Hg, mean (SD) = 8.00 (3.23) $PaCO_2$ (mmHg), mean (SD) 44.84 (7.57) Heterogeneous emphysema = 91/93 (97.8%) BL for LVRS & control groups were similar.			short form (SF-36)[9]	Physical functioning = 25.94 (95% CI 14.36 to 37.52; p=0.001) significant improvement in favour of LVRS Role physical = 12.70 (95% CI -7.45 to 32.84; p=0.217) non-significant (ns) Bodily pain = 2.80 (95% CI -16.43 to 10.82; p=0.687) ns General health = 14.80 (95% CI 5.62 to 23.98; p=0.002) sig. imp. in favour of LVRS Vitality = 10.00 (95% CI 1.30 to 18.71; p=0.024) sig. imp. in favour of LVRS Social functioning = 8.13 (95% CI -8.35 to 24.62; p=0.334) ns Role emotional = 10.40 (95% CI -32.31 to 11.52; p=0.352) ns Mental health = 6.58 (95% CI -0.91 to 14.07; p=0.085) ns Physical component = 6.90 (95% CI 2.86 to 10.94; p=0.001) sig. imp. in favour of LVRS Mental component = 0.56 (95% CI -6.11 to 4.99; p=0.844) ns			systematic review. 6/54 (11%) LVRS patients had VATS rather than open surgery, but results are not presented for open surgery alone and as the majority of LVRS patients (89%) had open surgery it is assumed that these results are indicative of outcomes for open surgery.

[9] The SF-36 is a widely used, validated, generic measure of health status which assesses QoL across eight domains, which are both physically and emotionally based. The eight domains are: physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; emotional well-being; social functioning; pain; general health. Scores are presented as a scale from 0 to 100. A high score indicates a more favourable health state.

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
					Forced expiratory volume in one second (FEV_1), mL	At BL (mean, SD): LVRS (n=54) = 693 (23.4) Control (n=39) = 683 (23.9) At 6 months (mean, SD): LVRS (47) = 885 (32) Control (34) = 613 (22) wmd = 167 (95% CI 29 to 304; p=0.017) in favour of LVRS			
					Total lung capacity (TLC), mL	At BL (mean, SD): LVRS (n=54) = 8,030 (164) Control (n=39) = 7,660 (130) At 6 months (mean, SD): LVRS (47) = 7,037 (123) Control (34) = 7,543 (131) wmd = -1.044 (95% CI -1,483 to -605; p<0.001) in favour of LVRS			
					Residual volume (RV), mL	At BL (mean, SD): LVRS (n=54) = 5,563 (262) Control (n=39) = 5,250 (247) At 6 months (mean, SD): LVRS (47) = 4,212 (196) Control (34) = 5,205 (240) wmd = -1,342 (95% CI -1,844 to -840; p<0.001) in favour of LVRS			
					Partial pressure of carbon dioxide in arterial blood ($PaCO_2$), mm Hg	At BL (mean, SD): LVRS (n=54) = 45.00 (SD not reported) Control (n=39) = 44.62 (not reported) At 6 months (mean, SD): LVRS (47) = 42.1 (SD not reported) Control (34) = 45.9 (SD not reported) wmd = -3.7183 (95% CI -6.960 to -0.477; p=0.025) in favour of LVRS			

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
					Diffusion capacity of the lung for carbon monoxide (DLCO), mL/min/mm Hg	At BL (mean, SD): LVRS (n=54) = 7.58 (3.24) Control (n=39) = 8.63 (3.15) At 6 months (mean, SD): LVRS (47) = 8.69 (SD not reported) Control (34) = 7.51 (SD not reported) wmd = 0.9810 (95% CI -0.334 to 2.296; p=0.144) ns			
				Secondary Safety	Hospital deaths, n	51/54 LVRS patients underwent the procedure. 1/54 (1.85%) hospital deaths or 1/51 (1.96%) hospital deaths			
					Total deaths, n	Over a 6-month f/up: LVRS = 3/54 (3.6%) Control = 2/39 (5.1%) p-value not reported			
					Hospital admissions, n	Over 6-month f/up: Control = 14/28 (50%) patients for 38 hospitalisations in CLVR & 1/11 (9%) patients in OBEST LVRS = 18/30 (60%) patients for 27 readmissions in CLVR & 3/24 (12.5%) patients for 3 readmissions in OBEST p-value for differences not reported.			
				Secondary Hospital utilisation	Length of hospital stay after surgery, days	Median = 22 days (range 4 to 161 days) in CLVR & 12 days (range 4 to 57) in OBEST			
Naunheim et al (2006) National	P1 Randomised controlled trial	n = 1218 Severe emphysema	n = 608 LVRS of which 580 (95.4%) underwent	Primary Clinical effectiveness	% of patients with an improvement in maximum	All patients (n=1218) LVRS = 23%, 15%, and 9% at 1, 2, and 3 years, respectively Control = 5%, 3%, and 1%	9	Direct	Before randomisation, eligible patients completed 6 to 10 weeks of pulmonary rehabilitation.

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Emphysema Treatment Trial (NETT) Data on 30 & 90 day mortality risk taken from Fishman et al (2003). Data on complications taken from McKenna et al (2004). USA Multicentre	Recruitment = 1998-2002 Median f/up=4.3 years	Entry criteria: FEV_1 ≤45% pred TLC ≥100% pred; RV ≥150% pred; $PaCO_2$ ≤60 mmHg; PaO_2 ≥45 mmHg; ability to walk ≥140 metres in 6 minutes; ability to complete 3 mins on a bicycle ergometer; abstinence from smoking Exclusion criteria: concurrent medical conditions precluding surgery or that might interrupt follow-up. In May 2001, patients with FEV1 ≤20% pred and either homogenous emphysema or DLCO ≤20% pred were found to be at high risk of dying after LVRS, with a low probability of functional benefit, and were no longer deemed to be eligible for	surgery, 406 (70%) by MS & 174 (30%) by VATS Plus usual medical care including pulmonary rehabilitation. n = 610 control Usual medical care (medical therapy and pulmonary rehabilitation)		work[10], Watts Defined as increase in maximum work of >10 Watts	OR = 5.79 (p<0.001) at 1 year OR = 5.06 (p<0.001) at 2 years OR = 7.43 (p<0.001) at 3 years Average initial improvements (time point not defined) of 5.4 Watts in surviving LVRS patients and decline by 4.4 Watts in control patients. Non-high-risk patients (n=1078) LVRS = 24%, 17%, and 10% at 1, 2, and 3 years, respectively Control = 5%, 4%, and 1% OR = 5.72 (p<0.001) at 1 year OR = 5.41 (p<0.001) at 2 years OR = 9.46 (p<0.001) at 3 years High-risk patients (n=140) LVRS = 11%, 7%, and 2% at 1, 2, and 3 years, respectively Control = 1%, 3%, and 2% OR = 8.90 (p=0.03) at 1 year OR = 2.62 (p=0.44) at 2 years OR = 0.83 (p>0.99) at 3 years The following sub-groups exclude high-risk patients: Upper-lobe-predominant and low baseline exercise capacity (n=290) LVRS = 42%, 30%, and 21% at 1, 2, and 3 years, respectively Control = 6%, 2%, and 0% OR = 12.5 (p<0.001) at 1 year OR = 26.1 (p<0.001) at 2 years p<0.001 at 3 years Upper-lobe-predominant and high exercise capacity (n=419) LVRS = 23%, 16%, and 10% at 1, 2, and 3 years, respectively			Randomisation methods not described. Patients not blinded. No mention of whether outcome assessors were blinded. 174/580 (30%) LVRS patients had VATS rather than open surgery, but results are not presented for open surgery alone and as the majority (70%) of LVRS patients had open surgery it is assumed that these results are indicative of outcomes for open surgery. Among the 608 patients assigned to LVRS, 95.4% received surgery, 3.5% refused surgery, and 1.2% were judged unsuitable for surgery after randomisation. Among the 610 patients assigned to medical treatment, 7.2% were known to have received LVRS outside of NETT, and 3.1% were known to have received lung transplants during follow-up. Of the surviving patients, 70% participated in the extension of follow-up and 76% participated in the mailed QoL data

[10] A measure of integrated cardiopulmonary and physical performance. It is determined by maximal, incremental, symptom-limited exercise using a cycle ergometer. The maximum work load is the highest work level reached (measured in Watts) and maintained for a full minute.

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		randomisation BL characteristics: Age years, mean (sd): LVRS = 66.5 (6.3) & control = 66.7 (5.9) Males, n (%): LVRS = 355 (58) & control = 391 (64) FEV_1 % pred, mean (sd): LVRS = 26.8 (7.4) & control = 26.7 (7.0) RV % pred, mean (sd): LVRS = 220.5 (49.9) & control = 223.4 (48.9) DLCO % pred, mean (sd): LVRS = 28.3 (9.7) & control = 28.4 (9.7) $PaCO_2$ (kPa), mean (sd): LVRS = 43.3 (5.9) & control = 43.0 (5.8) Upper-lobe predominant emphysema, n (%): LVRS = 385 (63) & control = 405 (67)				Control = 5%, 4%, and 2% OR = 5.99 (p<0.001) at 1 year OR = 4.79 (p<0.001) at 2 years OR = 5.26 (p=0.007) at 3 years Non-upper-lobe-predominant and low baseline exercise capacity (n=149) LVRS = 16%, 14%, and 2% at 1, 2, and 3 years, respectively Control = 9%, 7%, and 0% OR = 2.05 (p=0.3) at 1 year OR = 2.11 (p=0.27) at 2 years p>0.99 at 3 years Non-upper-lobe-predominant and high baseline exercise capacity (n=220) LVRS = 9%, 3%, and 3% at 1, 2, and 3 years, respectively Control = 4%, 4%, and 2% OR = 2.57 (p=0.22) at 1 year OR = 0.91 (p>0.99) at 2 years OR = 1.79 (p>0.99) at 3 years			collection reported in Naunheim et al 2006. ITT analysis carried out. High-risk patients defined as FEV_1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted. These were excluded from sub-group analyses. Relatively small sample size for sub-group analyses. Results for the NET trial are taken from the most recent main NETT paper with longest follow-up (Naunheim et al 2006), except for results on early mortality and complications, which were not reported in that paper, but were reported in earlier NETT papers (Fishman et al 2003 for mortality results and McKenna et al 2004 for complications). Results for early mortality and complication outcomes only, have been taken from these earlier NETT papers (Fishman et al 2003 and McKenna et al 2004), as these outcomes were not reported in the other included studies and it was felt that they are critical to assessing the
					QoL measured by % of patients with an improvement in St. George's Respiratory Questionnaire (SGRQ)[11] Defined as decrease in SGRQ score of >8 units	All patients (n=1218) LVRS = 40%, 32%, 20%, 10%, and 13% at 1, 2, 3, 4, and 5 years respectively Control = 9%, 8%, 8%, 4%, and 7% OR = 6.50 (p<0.001) at 1 year OR = 5.27 (p<0.001) at 2 years OR = 3.06 (p<0.001) at 3 years OR = 2.63 (p=0.05) at 4 years OR = 2.16 (p=0.12) at 5 years Average initial improvements (time point not defined) of 10.7 units in surviving LVRS patients and decline of 2.2 units in control. Non-high-risk patients (n=1078) LVRS =43%, 35%, 22%, 12%, and 15% at 1, 2, 3, 4, and 5 years, respectively			

[11] SGRQ is a validated, disease related, self-administered, measure of QoL. It contains 50-items covering symptoms, activities and psychosocial impact.

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		Heterogeneous emphysema, n (%): LVRS = 330 (54) & control = 336 (55) Similar baseline characteristics except for a higher proportion of men in control				Control=10%, 9%, 8%, 5%, and 7% OR = 6.72 (p<0.001) at 1 year OR = 5.33 (p<0.001) at 2 years OR = 3.26 (p<0.001) at 3 years OR = 2.80 (p=0.003) at 4 years OR = 2.32 (p=0.08) at 5 years High-risk patients (n=140) LVRS = 20%, 11%, 6%, 0%, and 0% at 1, 2, 3, 4, and 5 years, respectively Control = 4%, 1%, 3%, 0%, and 0% OR = 5.58 (p=0.01) at 1 year OR = 8.90 (p=0.03) at 2 years OR = 1.78 (p=0.69) at 3 years The following sub-groups exclude high-risk patients: Upper-lobe-predominant and low baseline exercise capacity (n=290) LVRS = 52%, 44%, 29%, 15% and 19% at 1, 2, 3, 4 and 5 years, respectively Control = 7%, 10%, 9%, 6% and 0% OR = 13.70 (p<0.001) at 1 year OR = 7.01 (p<0.001) at 2 years OR = 4.27 (p<0.001) at 3 years OR = 2.64 (p=0.11) at 4 years p=0.01 at 5 years Upper-lobe-predominant and high exercise capacity (n=419) LVRS = 48%, 41%, 31%, 17% and 23% at 1, 2, 3, 4 and 5 years, respectively Control = 12%, 10%, 9%, 4% and 13% OR = 6.96 (p<0.001) at 1 year OR = 6.46 (p<0.001) at 2 years OR = 4.73 (p<0.001) at 3 years OR = 4.58 (p=0.003) at 4 years OR = 2.12 (p=0.27) at 5 years Non-upper-lobe-predominant and low baseline exercise capacity (n=149) LVRS = 33%, 27%, 9%, 10% and 0% at 1, 2, 3,			effectiveness of LVRS. In Naunheim et al (2006) any outcomes are only reported as dichotomised endpoints e.g. number of participants improving in maximal exercise rather than absolute values. In McKenna et al (2004) when calculating the percentages for each length category for air leak, ICU stay and mechanical ventilation, it appears that data for patients who died within 30 days of surgery were excluded from the numerator but were included in the denominator.

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						4 and 5 years, respectively Control = 11%, 6%, 4%, 0% and 0% OR = 4.14 (p=0.002) at 1 year OR = 5.53 (p=0.002) at 2 years OR = 2.69 (p=0.29) at 3 years p=0.13 at 4 years Non-upper-lobe-predominant and high baseline exercise capacity (n=220) LVRS = 28%, 19%, 10%, 2% and 0% at 1, 2, 3, 4 and 5 years, respectively Control = 10%, 9%, 9%, 7% and 9% OR = 3.61 (p=0.001) at 1 year OR = 2.35 (p=0.07) at 2 years OR = 1.04 (p>0.99) at 3 years OR = 0.28 (p=0.33) at 4 years p=0.49 at 5 years			
				Secondary Resources	Percentage hospitalised, living in a nursing or rehabilitation facility, or unavailable for interview but not known to be dead	At 1 month: LVRS = 28.1% Control = 2.2% p<0.001 At 2 months: LVRS = 14.3% Control = 3.3% p<0.001 At 4 months: LVRS=6.7% Control = 3.2% p=0.007 At 8 months: LVRS = 3.3% Control = 3.7% p=0.87			
				Secondary Safety	Total mortality risk	Over 5 years f/up (medium f/up = 4.3 years) All patients (n=1218) LVRS = 0.11 deaths per person-year			

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Control = 0.13 deaths per person-year Overall RR = 0.85 (p=0.02) Non-high-risk patients (n=1078) LVRS = 0.10 deaths per person-year Control = 0.12 deaths per person-year Overall RR = 0.82 (p=0.02) High-risk patients (n=140) Overall RR = 1.14 (p=0.70) The following sub-groups exclude high-risk patients: Upper-lobe-predominant and low baseline exercise capacity (n=290) Overall RR = 0.57 (p= 0.01) in favour of LVRS Upper-lobe-predominant and high exercise capacity (n=419) Overall RR = 0.86 (p=0.19) Non-upper-lobe-predominant and low baseline exercise capacity (n=149) Overall RR = 0.80 (p=0.31) Non-upper-lobe-predominant and high baseline exercise capacity (n=220) Overall RR = 1.10 (p=0.79)			
					30-day mortality risk (Fishman et al 2003)	Non-high-risk patients (n=1078) LVRS = 2.2% Control = 0.2% Difference between groups p<0.001			
					90-day mortality risk (Fishman et al 2003)	All patients (n=1218) LVRS = 48/608 (7.9%; 95% CI 5.9 to 10.3) Control = 8/610 (1.3%; 95% CI 0.6 to 2.6) Difference between groups p<0.001 Non-high-risk patients (n=1078) LVRS = 28/538 (5.2%; 95% CI 3.5 to 7.4) Control = 8/540 (1.5%; 95% CI 0.6 to 2.9)			

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Difference between groups p=0.001 High-risk patients (n=140) LVRS = 20/70 (28.6%; 95% CI 18.4 to 40.6) Control = 0/70 (0%; 95% CI 0 to 5.1) Difference between groups p=<0.001 The following sub-groups exclude high-risk patients: Upper-lobe-predominant and low baseline exercise capacity (n=290) LVRS = 4/139 (2.9%; 95% CI 0.8 to 7.2) Control = 5/151 (3.3%; 95% CI 1.1 to 7.6) Difference between groups p=1.00 Upper-lobe-predominant and high exercise capacity (n=419) LVRS = 6/206 (2.9%; 95% CI 1.1 to 6.2) Control = 2/213 (0.9%; 95% CI 0.1 to 3.4) Difference between groups p=0.17 Non-upper-lobe-predominant and low baseline exercise capacity (n=149) LVRS = 7/84 (8.3%; 95% CI 3.4 to 16.4) Control = 0/65 (0%; 95% CI 0 to 5.5) Difference between groups p=0.02 Non-upper-lobe-predominant and high baseline exercise capacity (n=220) LVRS = 11/109 (10.1%; 95% CI 5.1 to 17.3) Control = 1/111 (0.9%; 95% CI 0.02 to 4.9) Difference between groups p=0.003			
					Intraoperative complications, % (McKenna et al 2004)	Non-high risk open LVRS by MS patients (n=359): Any intraoperative complication = 7% Hypotension = 0.3% Arrhythmia = 1.7% Hypoxaemia = 0.8% Hypercarbia = 0.8% Cardiac arrest = 0.3%			

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Uncontrolled air leak = 0.8% Other complications = 3.3% Only percentages were reported. The mean blood loss during open LVRS = 138.0 ml Patients needing a transfusion = 3.1%			
					Postoperative complications, % (McKenna et al 2004)	Non-high risk open LVRS by MS patients (n=359): Any postoperative complication = 58.4% Arrhythmia = 21.3% Pneumonia = 20.1% Tracheostomy = 9.2% Failure to wean from ventilation = 6.1% Urinary retention = 4.2% Failure of early extubation = 3.1% Atrial fibrillation = 2.5% Reoperation for air leak = 2.2% Readmission within 72 hours after discharge = 2.2% Sepsis = 2% Epidural catheter complications = 1.1% Mediastinitis = 0.8% Sternal debridement = 0.8% Pulmonary embolus = 0.6% Air leak at closure results (n=359): None = 45.7% Occasional bubble or pinhole stream = 37.3% Intermediate stream of bubbles with respiratory variation = 14.2% Large stream of nearly constant bubbles = 2.8% Days with air leak in the 30 days after surgery (n=339): 0 days with air leak = 10.9% 1-6 days with air leak = 40.1% 7-14 days with air leak = 21.5% 15-29 days with air leak = 14.8% 30 days with air leak = 9.7%			

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
						Dead within 30 days of LVRS = 3.0% (excluded from above results) Days in Intensive Care Unit (ICU) (n=354): 0-1 days in ICU = 43.5% 2 days in ICU =15.3% 3-29 days in ICU =36.2% 30 days in ICU =2.3% Dead within 30 days of LVRS = 2.8% (excluded from above results) The reason for not including the full 359 patients is not reported. Days on mechanical ventilation (n=357) 0 days on ventilator = 76.2% 1 days on ventilator =6.4% 2-14 days on ventilator = 6.2% 15-29 days on ventilator = 7.6% 30 days on ventilator = 0.8% Dead within 30 days of LVRS = 2.8% (excluded from above results) The reason for not including the full 359 patients is not reported. Only percentages were reported.			
Hillerdal et al (2005) Sweden Multicentre	P1 Randomised controlled trial Recruitment = 1997 to 2000 F/up = 12 months	n=106 Severe emphysema; FEV1 of ≤35%; CT scan showing diffuse emphysema and areas of more severe local involvement on CT and/or scintigraphy; age≤75 years Excessive	n=53 LVRS of which 49 (92.4%) underwent surgery, 42 (86%) by MS, 3 (6%) by VATS & 4 (8%) by thoracotomy. Plus physical training for 3 months n=53 controls	Primary Clinical effectiveness	QoL measured by SGRQ	Age-sex adjusted mean differences of changes from BL to endpoint between the groups: At 6 months: Total score: -14.3 (95% CI -19.7 to -9.0) Symptoms: -11.7 (95% CI -20.2 to -3.3) Activity: -16.8 (95% CI -23.1 to -10.5) Impact: -13.1 (95% CI -19.2 to -7.0) At 12 months: Total score: -8.8 (95% CI -17.6 to -0.04) Symptoms: -17.1 (95% CI -22.7 to -11.6) Activity: -14.6 (95% CI -20.0 to -9.1) Impact: -14.7 (95% CI -19.7 to -9.8) All in favour of LVRS.	8	Direct	Before randomisation, eligible patients completed an intense physical training program for a minimum of 6 weeks. Randomisation methods are clearly described and appear adequate. Difference in male proportion between groups at baseline. These were adjusted for in analyses. Blinding not described.

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		hyperinflation with an RV ≥ 200% Major exclusions: Homogenous emphysema; other diseases e.g. heart disease, asthma or bronchitis; smoking; DLCO ≤20% pred; sequelae of pleurisy/pleural adhesions; long-term treatment with oral steroids and/or Cushingoid habitus; other factors that make surgery, rehabilitation, or follow-up impossible or difficult After the safety committee reviewed the data of the first five patients who died after surgery, a DLCO of ≤20% pred was added as an exclusion criterion. BL characteristics: Males n=45 (42%)	Physical training for 1 year. Biweekly small group physical training sessions (bicycle ergometer & muscle strength exercise) plus home exercise program at least 3 times a week.		QoL measured by SF-36	Age-sex adjusted mean differences of changes from BL to endpoint between the groups: At 6 months: Physical functioning: 17.1 (95% CI 9.8 to 24.5) Role physical: 20.5 (95% CI 3.1 to 37.9) Bodily pain: 3.1 (95% CI -5.3 to 13.1; ns) General health: 6.8 (95% CI 0.2 to 13.4) Vitality: 11.0 (95% CI 1.3 to 20.6) Social functioning: 8.5 (95% CI -5.5 to 22.5; ns) Role emotional: 10.2 (95% CI -6.7 to 27.0; ns) Mental health: 7.3 (95% CI -1.6 to 16.1; ns) At 12 months: Physical functioning: 19.7 (95% CI 12.1 to 27.3) Role physical: 25.2 (95% CI 7.7 to 42.6) Bodily pain: 9.1 (95% CI -0.3 to 18.6; ns) General health: 9.7 (95% CI 3.2 to 16.2) Vitality: 11.4 (95% CI 1.2 to 21.6) Social functioning: 21.0 (95% CI 6.2 to 35.7) Role emotional: 9.7 (95% CI -11.0 to 30.6; ns) Mental health: 13.6 (95% CI 5.2 to 22.0) All in favour of LVRS.			LVRS was performed on 49 of the 53 patients randomised to surgery. Three patients deteriorated, one of whom underwent transplantation, and one patient no longer wished to undergo surgery. In the control group, 2 patients withdrew their consent, 2 patients deteriorated and were unable to participate in the training program, and 2 patients acquired other diseases (heart disease and pulmonary fibrosis, respectively). Two control patients underwent LVRS during the follow-up period because of rapid deterioration ITT was carried out. 3/49 (6%) LVRS patients had VATS rather than open surgery, but results are not presented for open surgery alone and as the majority (94%) of LVRS patients had open surgery it is assumed that these results are indicative of outcomes for open surgery.
				Secondary Clinical effectiveness	Incremental shuttle walk distance (ISWD), metres[12]	Age-sex adjusted mean differences of changes from BL to endpoint between the groups: At 6 months: md = 104 (95% CI 57 to 151) At 12 months md = 90 (95% CI 47 to 133) In favour of LVRS.			
					Maximum work, Watts	Age-sex adjusted mean differences of changes from BL to endpoint between the groups:			

[12] The incremental shuttle walking distance (ISWD) is a progressive exercise test where patients walk 10 metres at a set speed. After each 10 metres, the speed is increased in a standardised manner until point of intolerance. It measures total distance walked.

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
		Age, years (mean) = 62 FEV1, % pred, (mean) = 26% RV, % pred (mean) = 261%				At 6 months: md = 11 (95% CI 4 to 18) At 12 months md = 9 (95% CI 0 to 18) In favour of LVRS.			
					FEV_1, L	Age-sex adjusted mean differences of changes from BL to endpoint between the groups: At 6 months: md = 0.23 (95% CI 0.14 to 0.31) At 12 months md = 0.19 (95% CI 0.09 to 0.28) In favour of LVRS.			
					Vital capacity (VC), L	Age-sex adjusted mean differences of changes from BL to endpoint between the groups: At 6 months: md = 0.45 (95% CI 0.18 to 0.72) At 12 months md = 0.39 (95% CI 0.13 to 0.65) In favour of LVRS.			
					RV, L	Age-sex adjusted mean differences of changes from BL to endpoint between the groups: At 6 months: md = -0.94 (95% CI -1.37 to 0.52; ns) At 12 months md = -1.00 (95% CI -1.37 to -0.62) In favour of LVRS.			

Use of open lung volume reduction surgery vs maximal medical therapy									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
					TLC, L	Age-sex adjusted mean differences of changes from BL to endpoint between the groups: At 6 months: md = -0.36 (95% CI -0.80 to -0.08) At 12 months md = -0.48 (95% CI -0.91 to -0.05) In favour of LVRS (greater fall in TLC in LVRS group).			
				Secondary Safety	Total mortality, n	Over 12 months f/up: LVRS = 7/53 (13%) Control = 2/53 (4%) Difference = ns (p=0.489)			
					Hospital deaths after surgery, n	6 in-hospital deaths occurred after surgery (12%) caused by pneumonia and respiratory failure (on days 9, 15, 19, 42, 49, and 71).			

Definition of abbreviations: 6MWD = 6-minute-walk distance; % pred = % predicted; BL = baseline; CI = confidence interval; CLVR = Canadian Lung Volume Reduction; CRDQ = Chronic Respiratory Disease Questionnaire; DLCO = diffusing capacity of carbon monoxide; FEV_1 = forced expiratory volume in one second; f/up = follow-up; ISWD = incremental shuttle walking distance; ITT = intention-to-treat; L = litres; LVRS = lung volume reduction surgery; NETT = National Emphysema Treatment Trial; ns = non-significant; OBEST = Overholt-Blue Cross Emphysema Surgery Trial; $PaCO_2$ = partial pressure of carbon dioxide in arterial blood; PaO_2 = partial pressure of oxygen in arterial blood; QoL = quality of life; RCT = randomised controlled trial; RV = residual volume; TLC = total lung capacity; SD = standard deviation; SE = standard error; SGRQ = St George's Respiratory Questionnaire; SF-36 = Short Form 36 item; VATS = video assisted thoracoscopic surgery; wmd = weighted mean difference

Cost-effectiveness studies									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Ramsey et al (2007) USA	S2 Secondary analysis of existing data	n=1066 Patients enrolled in NETT (Naunheim et al 2006). Excludes high-risk group (patients with FEV1 ≤20% pred and either homogenous emphysema or DLCO ≤20% pred) who were found to be at high risk of dying after LVRS, with a low probability of functional benefit partway through trial, and were no longer deemed to be eligible for randomisation (n=140) Excludes patients not enrolled with Medicare (n=12)	n = 531 LVRS (around 70% had MS) n = 535 control Usual medical care	Primary Cost-effectiveness	Cost per quality adjusted life year (QALY)	All patients: At 5-years: $140,000 per QALY (95% CI 40,155 to 239,359) At 10-years: $54,000 per QALY gained (confidence intervals not reported) In patients with upper-lobe predominant emphysema and low exercise capacity: At 5-years: $77,000 per QALY (CIs not reported) At 10-years: $48,000 per QALY (CIs not reported) In patient with upper-lobe predominant emphysema and high exercise capacity At 5-years: $170,000 per QALY (CIs not reported) At 10-years: $40,000 per QALY (CIs not reported) In patients with non-upper-lobe predominant emphysema and low exercise capacity At 5-years: $225,000 per QALY (CIs not reported) At 10-years: $87,000 per QALY (CIs not reported) No results reported for patients with non-upper-lobe predominant emphysema and high exercise capacity.	9	Direct	10-year results will have a large range of uncertainty as based on estimates of survival and QoL based on 5-year results. Some of the LVRS group (around 30%) had VATS and this type of surgery is likely to have different costs to open surgery. Small sample size for sub-group analyses. Results based on a trial where patients, and possibly also outcome assessors, were not blinded, therefore results may be influenced by placebo effect. Administrative and facility costs associated with the maintenance of an LVRS centre not included. Costs are over ten years old. Cost per QALY gained from a societal perspective were reported. Costs were from a US setting and included medical goods and services, transportation to and from health-care facilities, time spent by family and friends caring for the patient, and time spent in treatment. Costs were estimated using Medicare claims and clinical trial reporting forms.

Cost-effectiveness studies									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
									QALYs were derived by adjusting survival by health-state preferences, also known as utilities, which range from 0 (death) to 1.0 (optimum quality of life). Utility weights were obtained from the Quality of Wellbeing Scale (QWB).[13] Costs and benefits after year one were discounted at 3% per annum.
Miller et al (2006) Canada	S2 Secondary analysis of existing data	n=59 Patients recruited into CLVR with follow-up data	n=31 LVRS n=28 Control	Primary Cost-effectiveness	Cost per QALY	Over 2-years Mean cost per patient Canadian $ LVRS = 49,776 Control = 21,657 QALYs gained: LVRS=1.29 Control=1.08 Cost per QALY = 133,900 Canadian $ per QALY (95% CI 26,000 to undefined)	8	Direct	QALYs were calculated using Health Utility Index (HUI3) data collected over 2 years in the CLVR trial. This data is taken from a trial with a small sample size and short follow-up. Only outcomes assessors were blinded. Costs were from a Canadian setting and included surgery, hospital stay, intensive care unit stay, GP visits, ER visits, specialist visits, oxygen use and rehabilitation. Costs are ten years old.

Definition of abbreviations: CI = confidence interval; CLVR = Canadian Lung Volume Reduction; DLCO = diffusing capacity of carbon monoxide; FEV_1 = forced expiratory volume in one second; LVRS = lung volume reduction surgery; NETT = National Emphysema Treatment Trial; QALY = quality adjusted life year; QoL = quality of life; QWB = Quality of Wellbeing;

[13] The Quality of Wellbeing Scale consists of 71 items which measure overall health status and QoL over the previous three days in four areas: physical activities, social activities, mobility, and symptom/problem complexes.

8 Grade of evidence table

Use of open lung volume reduction surgery vs maximal medical therapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
QoL – St. George's Respiratory Questionnaire	Naunheim et al (2006) Hillerdal et al (2005)	9 8	Direct	A	St. George's Respiratory Questionnaire (SGRQ) is a validated, disease related, self-administered, measure of quality of life (QoL). It contains 50-items covering symptoms, activities and psychosocial impact. The best study, Naunheim et al (2016), reported on the percentage of patients with a clinically significant improvement in SGRQ which is defined as a decrease in SGRQ score of >8 units over five years. Amongst all patients (n=1,218), 40%, 32%, 20%, 10%, and 13% of lung volume reduction surgery (LVRS) patients improved in SGRQ at 1, 2, 3, 4, and 5 years respectively compared to 9%, 8%, 8%, 4%, and 7% control patients. This represents odds ratios (ORs) of 6.50 (p<0.001), 5.27 (p<0.001), 3.06 (p<0.001), 2.63 (p=0.05) and 2.16 (p=0.12) at 1, 2, 3, 4, and 5 years respectively. An average initial improvement (time point not defined) of 10.7 units in surviving LVRS patients and a decline of 2.2 units in control patients were reported. Mean values were not reported for other time points. Minimal clinically important differences (MCID) range from 2 to 8 points in the literature (Jones et al 2014). Naunheim et al (2016) used a greater than 8-point decrease to define a change that is clinically important to patients. Therefore, these results show that LVRS offers clinically meaningful improvements in QoL as measured by the SGRQ for up to four years. LVRS patients were three times more likely to show an improvement in SGRQ than those in the control group at four years. These results are based on a well-conducted randomised controlled trial (RCT) with a large sample size (1,218) and long follow-up of five years. One issue is that it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely give positive responses and hence bias the results in favour of LVRS. Furthermore, 30% of the LVRS group had video assisted thoracoscopic surgery (VATS) rather than open surgery which may have affected the results. However, overall these results provide good evidence that open LVRS benefits patients in terms of QoL.
QoL - Medical Outcomes Study 36-item short form	Miller et al (2005) Hillerdal et al (2005)	8 8	Direct	A	The Medical Outcomes Study 36-item Short Form (SF-36) is a widely used, validated, generic measure of health status which assesses QoL across eight domains, which are both physically and emotionally based. The eight domains are physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health. Scores are presented as a scale from 0 to 100. A high score indicates a more favourable health state. It is not specific to respiratory diseases. The study with the longest follow-up, Hillerdal et al (2005), found statistically significant mean differences (of changes from baseline) between the groups for physical functioning (mean difference (md) = 17.1; 95% confidence intervals (95% CI) 9.8 to 24.5), role physical (md = 20.5; 95% CI 3.1 to 37.9), general health (md = 6.8; 95% CI 0.2 to 13.4) and vitality (md = 11.0; 95% CI 1.3 to 20.6), all in favour of LVRS at six months. Further improvements were seen at 12 months, with statistically significant mean differences (of changes from baseline) between the groups of 19.7 (95% CI 12.1 to 27.3) for physical functioning, 25.2 (95% CI 7.7 to 42.6) for role physical, 9.7 (95% CI 3.2 to 16.2) for general health, 11.4 (95% CI 1.2 to 21.6) for vitality, 21.0 (95% CI 6.2 to 35.7) for social functioning and 13.6 (95% CI 5.2 to 22.0) for mental health, all in favour of LVRS. These results show that LVRS improves QoL in the majority of the domains measured by the SF-36 up to 12

Use of open lung volume reduction surgery vs maximal medical therapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					months. No standard MCID has been established for SF-36. One of the included studies in this review defined 5 to be a small change in score and 10 to be a moderate-to-large change in score (Miller et al 2005), and based on this definition, there is evidence to suggest a moderate to large clinically significant effect on QoL with LVRS. These results are based on an RCT with a relatively small sample size (n=106) and short follow-up of 12 months, therefore there is a large range of uncertainty around the estimated effect sizes and the long-term impacts are not known. In addition, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to give positive responses and hence bias the results in favour of LVRS. Furthermore, SF-36 is a general measure of QoL so may be less responsive than measures of QoL specifically for people with respiratory disease. Therefore, these results should be treated with caution.
QoL- Chronic Respiratory Disease Questionnaire	Miller et al (2005)	8	Direct	B	Chronic Respiratory Disease Questionnaire (CRDQ) is a patient reported, disease specific measure of QoL which focuses on four domains: dyspnoea, fatigue, emotional function, and mastery (patients' sense of being in control of their lives and their health problem). At six months, Miller et al (2005) found statistically significant improvements with LVRS compared to medical management in all four domains of the CRDQ which included dyspnoea (md = 1.56; 95 CI 0.80 to 2.32; p=0.001), fatigue (md=1.17; 95 CI 0.62 to 1.71; p=0.001), mastery (md = 1.19; 95 CI 0.63 to 1.74; p= 0.001) and emotion (md = 0.87; 95 CI 0.28 to 1.46; p=0.004). The difference observed between the two groups across all the CRDQ domains at six months was greater than the widely reported MCID of 0.5 (Goldstein et al 2005). Therefore, there is evidence to support a clinically meaningful improvement in QoL as measured by CRDQ with open LVRS in the short-term. These results are based on a meta-analysis of two RCTS with a relatively small pooled sample size (n=93) and short follow-up of six months and therefore there is a large range of uncertainty around the estimated effect sizes and the long-term impacts are not known. In addition, it was not possible to blind the patients to their allocated treatment in the trials so patients in the intervention group may be more likely to give positive responses and hence bias the results in favour of LVRS. Therefore, these results should be treated with caution.
Exercise capacity – Maximum work, Watts	Naunheim et al (2006) Hillerdal et al (2005)	9 8	Direct	A	A measure of integrated cardiopulmonary and physical performance. It is determined by maximal, incremental, symptom-limited exercise using a cycle ergometer. The maximum work load is the highest work level reached (measured in Watts) and maintained for a full minute. It is a useful indicator of how severely capacity for exercise is limited and it helps to indicate capacity to do everyday tasks. The best study, Naunheim et al (2016), reported on the percentage of patients with an improvement in maximum exercise capacity (defined as increase in maximum work of >10 Watts). Amongst all patients (n=1,218), 23%, 15%, and 9% of LVRS patients improved in maximum exercise capacity at 1, 2 and 3 years respectively compared to 5%, 3%, and 1% of control patients. This represents statistically significant ORs of 5.79 (p<0.001), 5.06 (p<0.001), 7.43 (p<0.001) at 1, 2 and 3 years respectively in favour of LVRS. An average initial improvement (time point not defined) of 5.4 Watts in surviving LVRS patients and a decline by 4.4 Watts in control patients were reported. Naunheim et al (2016) used 10 Watts or greater increase to define a change that is clinically important to patients. Therefore, these results show that LVRS offers clinically meaningful improvements in exercise capacity as

Use of open lung volume reduction surgery vs maximal medical therapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					measured by cycle ergometer maximum exercise capacity tests for up to three years. These results are based on a well-conducted RCT with a large sample size (1,218) and long follow-up of five years. One issue is that it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to try harder in the tests and hence bias the results in favour of LVRS. Furthermore, 30% of the LVRS group had VATS rather than open surgery which may have affected the results. However, overall these results provide good evidence that open LVRS benefits patients in terms of exercise capacity.
Exercise capacity - Six-minute walk distance, feet	Miller et al (2005)	8	Direct	B	The six-minute walk distance (6MWD) is defined as the distance that a patient can walk in six minutes usually on a treadmill. Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise, including walking. The distance that a patient can walk in six minutes is a useful indicator of how severely capacity for exercise is limited and it helps to indicate capacity to do everyday tasks. Miller et al (2005) reported a statistically significant mean difference between LVRS and medical management group of 148.8 feet (95% CI 24.3 to 273.2; p=0.019) in favour of LVRS at six months. A 26 metre (85 feet) improvement is most widely considered to be the MCID for 6MWD (Jones et al 2014). Therefore, these results show that LVRS offers a clinically meaningful improvement in exercise capacity as measured by the 6MWD for up to six months in patients with severe emphysema. These results are based on a meta-analysis of two RCTS with a relatively small pooled sample size (n=93) and short follow-up of six months and therefore there is a large range of uncertainty around the estimated effect size with a possibility of the true effect being lower than the MCID. In addition, it was not possible to blind the patients to their allocated treatment in the trials so patients in the intervention group may be more likely to try harder in the tests and hence bias the results in favour of LVRS. Therefore, these results should be treated with caution.
Exercise capacity – Incremental shuttle walking distance, metres	Hillerdal et al (2005)	8	Direct	B	The incremental shuttle walking distance (ISWD) is a progressive exercise test where patients walk 10 metres at a set speed. After each 10 metres, the speed is increased in a standardised manner until point of intolerance. It measures total distance walked. Lung damage and breathlessness restricts the capacity of patients with severe emphysema to do exercise, including walking. The ISWD is a useful indicator of how severely capacity for exercise is limited and it helps to indicate capacity to do everyday tasks. Hillerdal et al (2005) found a statistically significant mean difference (of changes from baseline) between the groups of 104 metres (95% CI 57 to 151) at six months and 90 metres (95% CI 47 to 133) at 12 months in favour of LVRS. An MCID for ISWD is considered to be 47.5 metres (Jones et al 2014). Therefore, these results show that LVRS offers a clinically meaningful improvement in exercise capacity as measured by the ISWD up to 12 months in patients with severe emphysema. These results are based on an RCT with a relatively small sample size (n=106) and short follow-up of 12 months and hence there is a large range of uncertainty around the estimated effect sizes and the long-term impacts are not known. In addition, it was not possible to blind the patients to their allocated treatment so patients in the intervention group may be more likely to try harder in the tests and hence bias the results in favour of LVRS. Therefore, these results should be treated with caution.

Use of open lung volume reduction surgery vs maximal medical therapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Lung function – Forced expiratory volume in one second, litres	Miller et al (2005) Hillerdal et al (2005)	8 8	Direct	A	Forced expiratory volume in one second (FEV_1) is the maximal quantity of air a patient can exhale in one second. It is used as a measure of the severity of emphysema and to monitor response to treatment. If emphysema has caused large areas of the lung to lose their elasticity, less air can be exhaled quickly (in the first second of expiration) and hence FEV_1 is lower. It is expressed in litres or as percentage of predicted value (% predicted) based on age, size, sex and race. The study with the longest follow-up, Hillerdal et al (2005) reported a statistically significant mean difference (of changes from baseline) between the groups of 0.23 litres (95% CI 0.14 to 0.31) for FEV_1 at six months and 0.19 litres (95% CI 0.09 to 0.28) at 12 months in favour of LVRS. An increase of 0.1 litres is widely considered to be an MCID (Jones et al 2014). Therefore, these results show that LVRS offers a clinically meaningful improvement in lung function as measured by FEV_1 up to 12 months in patients with severe emphysema. These results are based on a RCT with a relatively small sample size (n=106) and short follow-up of 12 months hence there is a large range of uncertainty around the estimated effect sizes and the long-term impacts are not known.
Lung function – Total lung capacity, litres	Miller et al (2005) Hillerdal et al (2005)	8 8	Direct	A	Total lung capacity (TLC) includes the useful capacity of the lung and the RV or “dead space”. Emphysema damages lung and reduces its elasticity resulting in hyperinflation. This increases the TLC and RV while reducing overall lung function. The study with the longest follow-up, Hillerdal et al (2005), reported a statistically significant mean difference (of changes from baseline) of -0.36 litres (95% CI -0.80 to -0.08) at 6 months and -0.48 litres (95%CI -0.91 to -0.05) at 12 months in favour of LVRS. These results show that open LVRS offers a reduction in TLC in patients with severe emphysema. However, no MCID could be found in the papers reviewed so it is not clear if these changes are of clinical importance. These results are based on a RCT with a relatively small sample size (n=106) and short follow-up of 12 months hence there is a large range of uncertainty around the estimated effect sizes and the long-term impacts are not known.
Lung function – Residual volume, litres	Miller et al (2005) Hillerdal et al (2005)	8 8	Direct	A	Residual volume (RV) is the amount of air left in the lungs after full expiration and effectively represents the volume of “dead space” in the lung which does not help with gas exchange as air does not flow in and out. Lung damage and loss of elasticity in emphysema increases the RV. The study with the longest follow-up, Hillerdal et al (2005), reported a non-significant mean difference (of changes from baseline) between the groups of -0.94 litres (95% CI -1.37 to 0.52) at six months and a significant mean difference of -1.00 litres (95% CI -1.37 to -0.62) at 12 months in favour of LVRS. These results show that there is evidence to support a reduction in RV with open LVRS at 12 months but the results at six months are uncertain. Reductions of 350 ml and 430 ml have been defined in studies as MCIDs (van Agteren

Use of open lung volume reduction surgery vs maximal medical therapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					et al 2017) which would mean that the 12 month reduction of 1 litres would be clinically meaningful to patients. These results are based on a single RCT with a relatively small sample size (n=106) and short follow-up of 12 months hence there is a wide range of uncertainty around effect sizes and the long-term impacts are unknown.
Lung function – Vital capacity, litres	Hillerdal et al (2005)	8	Direct	B	Vital capacity (VC) is the maximum amount of air a person can expel from the lungs after a maximum inhalation and is another indicator of lung function. Hillerdal et al (2005) reported a statistically significant mean difference (of changes from baseline) of 0.45 litres (95% CI 0.18 to 0.72) for VC at six months and 0.39 litres (95% CI 0.13 to 0.65) at 12 months in favour of LVRS. These results show that open LVRS offers an increase in VC in patients with severe emphysema. However, no MCID was found in the literature so it is not clear if these improvements are clinically important. These results are based on a single RCT with a relatively small sample size (n=106) and short follow-up of 12 months hence there is a large range of uncertainty around the estimated effect sizes and the long-term impacts are not known.
Lung function – Diffusion capacity of the lung for carbon monoxide, ml/min/mm Hg	Miller et al (2005)	8	Direct	B	Emphysema damages lung tissue, reducing the diffusion capacity of the lung for oxygen and hence causing breathlessness. The diffusion capacity of the lung for carbon monoxide (DLCO) is a measure of this diffusion capacity of the lung for gases. Miller et al (2005) reported a non-significant mean difference for DLCO of 0.9810 mL/min/mm Hg (95% CI -0.334 to 2.296; p=0.144). LVRS was not shown to improve DLCO in patients with severe emphysema. These results are based on a meta-analysis of 2 RCTS with a relatively small pooled sample size (n=93) and short follow-up of six months. There is a wide range of uncertainty around the effect size and the long-term impacts are not known. Therefore the results should be treated with caution.
Lung function – Partial pressure of carbon dioxide in arterial blood, mm Hg	Miller et al (2005)	8	Direct	B	Carbon dioxide (CO_2) is produced through metabolic processes in the body and enters the blood. The lungs help to remove the CO_2 from the blood. Partial pressure of carbon dioxide in arterial blood ($PaCO_2$) is the pressure of CO_2 dissolved in the arterial blood and is a measure of how well the lungs are able to remove CO_2 from the blood. A reduction in $PaCO_2$ signifies an improvement in lung function. Miller et al (2005) reported a statistically significant mean difference for $PaCO_2$ of -3.7183 mm Hg (95% CI -6.960 to -0.477; p=0.025) in favour of LVRS. These results suggest that LVRS offers a reduction in $PaCO_2$ in patients with severe emphysema. However, no value for MCID so it is not clear if these improvements are clinically meaningful to patients. These results are based on a meta-analysis of 2 RCTS with a relatively small pooled sample size (n=93) and short follow-up of six months. There is a wide range of uncertainty around the effect size and the long-term impacts are

Use of open lung volume reduction surgery vs maximal medical therapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					not known.
Mortality - 30-day risk, %	Fishman et al (2003)	9	Direct	B	The 30-day mortality risk is the chance of a patient dying within 30 days after having LVRS. It is used as a measure of risk of death related to surgery. The effect of treatment on mortality is important, particularly for a treatment which, while improving some measures such as lung function, also results in serious adverse events and complications. In an earlier analysis of the NET trial (Naunheim et al 2016), Fishman et al (2003) reported that among the 1,078 patients who were not at high risk (excluding those with FEV_1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted), the 30-day mortality risk was 2.2% in the LVRS group compared with 0.2% in the control group (p<0.001). Results for all the patients in the trial and for the high-risk patients alone were not reported. There is evidence to suggest an increased risk of early mortality within 30 days after open LVRS in patients with severe emphysema. These results are based on a well-conducted RCT with a large sample size (1,218). One issue to note is that 30% of the LVRS group had VATS rather than open surgery which may have affected the results. Overall, however, the results provide good evidence of an increased risk of early mortality associated with open LVRS.
Mortality - 90-day risk, %	Fishman et al (2003)	9	Direct	B	The 90-day mortality risk is the chance of a patient dying within 90 days after having LVRS. It is used as a measure of risk of death that might be related to surgery. The effect of treatment on mortality is important, particularly for a treatment which, while improving some measures such as lung function, also results in serious adverse events and complications. In an earlier analysis of the National Emphysema Treatment Trial (NETT; Naunheim et al 2016), Fishman et al (2003) reported a 90-day mortality risk amongst all patients of 7.9% (95% CI 5.9 to 10.3) in the LVRS group and 1.3% (95% CI 0.6 to 2.60) in the control group. This represents a statistically significant higher risk with LVRS (p<0.001). Amongst non-high-risk patients, the risk was 5.2% (95% CI 3.5 to 7.4) in the LVRS group and 1.5% (95% CI 0.6 to 2.9) in the control group (p=0.001), and amongst high-risk patients it was 28.6% (95% CI 18.4 to 40.6) in LVRS group and 0% (95% CI 0 to 5.1) in control group. There is evidence to suggest an increased risk of mortality within 90-days of open LVRS. The risk was deemed too high for patients defined as high-risk (those with FEV_1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted) and these patients were stopped from being recruited into the trial partway through the trial. These results are based on a well-conducted RCT with a large sample size (1,218). One issue to note is that 30% of the LVRS group had VATS rather than open surgery which may have affected the results. Overall, however, the results provide good evidence of an increased risk of early mortality associated with open LVRS.
Mortality - In hospital risk, %	Miller et al (2005)	8	Direct	A	The risk of dying in hospital during LVRS or in hospital stay after LVRS. It is used as a measure of risk of death related to surgery. The effect of treatment on mortality is important, particularly for a treatment which, while

Use of open lung volume reduction surgery vs maximal medical therapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
	Hillerdal et al (2005)	8			improving some measures such as lung function, also results in serious adverse events and complications. The study with the slightly larger sample size, Hillerdal et al (2005) reported a in hospital mortality risk of 6/53 (12%) caused by pneumonia and respiratory failure (on days 9, 15, 19, 42, 49, and 71) in the LVRS group. No results for the control group were reported for the same time period. This result suggests a high rate of death in hospital after LVRS. However, this result is higher than the 30-day mortality rate reported in Naumheim et al 2006 of 2.2% (see above) which is based on larger numbers and is likely to be a more accurate figure. The results from Hillerdal et al are only based on 53 LVRS patients and it is not known whether they differ significantly to the mortality rate for control patients for the same time period so should be treated with caution.
Mortality – Total risk, deaths/person-year	Miller et al (2005)	9	Direct	A	The effect of treatment on overall mortality is important, particularly for a treatment which, while improving some measures such as lung function, also results in serious adverse events and complications. Over five years (4.3 years median follow-up), Naunheim et al (2006) reported a total mortality rate of 0.11 deaths per person-year in the LVRS group and 0.13 in the control group. This represents a statistically significant overall relative risk (RR) of 0.85 (p=0.02). The lowest mortality rate (overall RR = 0.57; p=0.01) was seen amongst patients with upper lobe predominant emphysema and low exercise capacity at baseline (excluding those at high-risk). This group of patients represented a quarter of the trial's population. These results show that LVRS improves overall survival compared to medical management. Patients with upper lobe predominant emphysema and low exercise capacity at baseline were shown to have the highest improvement in survival after LVRS. These results are based on a well-conducted RCT with a large sample size (1,218) and long follow-up of 5 years. One issue to note is that 30% of the LVRS group had VATS rather than open surgery which may have affected the results. Overall, however, the results provide good evidence of an increase in overall survival. It is an important result because it suggests that there is a benefit in overall longer-term survival despite the high initial risk of mortality post-surgery.
	Naunheim et al (2006)	9			
	Hillerdal et al (2005)	8			
Complications – Intraoperative, %	McKenna et al (2004)	9	Direct	B	Assessing complications arising during surgery is important as if serious and/or common they may outweigh the benefits associated with LVRS. An earlier publication of the NET trial on safety and effectiveness of LVRS by open surgery compared to video assisted thoracoscopic surgery (VATS) reported that 7% of open LVRS patients who were not at high-risk (n=359)[14] had intraoperative complications which included arrhythmia (1.7%), uncontrolled air leak (0.8%), hypoxaemia (0.8%), hypercapnia (0.8%), hypotension (0.3%), cardiac arrest (0.3%), and other complications (3.3%). Only percentages were reported, not number of patients (McKenna et al 2004). The mean blood loss during open LVRS was 138.0 ml and 3.1% of patients needed a transfusion.

[14] High risk defined as patients with FEV1 ≤20% predicted and either homogenous emphysema or DLCO ≤20% predicted.

Use of open lung volume reduction surgery vs maximal medical therapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
					These results suggest a moderate complication rate during open LVRS in patients with severe emphysema. However, the severity and long-term impact of this are not discussed, which makes it difficult to interpret the significance of this finding for patients. These results are taken from a large group of patients having open LVRS (n=359) from a well conducted RCT and therefore provide good evidence of complications associated with open LVRS.
Complications – postoperative, %	McKenna et al (2004)	9	Direct	B	Assessing complications arising after surgery is important as if serious and/or common they may outweigh the benefits associated with LVRS. An earlier publication of the NET trial on safety and effectiveness of LVRS by open surgery compared to video assisted thoracoscopic surgery (VATS) reported that 58.4% of open LVRS patients who were not at high-risk (n=359) had postoperative complications within 30 days after LVRS. These included arrhythmia (21.3%), pneumonia (20.1%), tracheostomy (9.2%), failure to wean from ventilation (6.1%), urinary retention (4.2%), failure of early extubation (3.1%), atrial fibrillation (2.5%), reoperation for air leak (2.2%), readmission within 72 hours after discharge (2.2%), sepsis (2%), epidural catheter complications (1.1%), mediastinitis (0.8%), sternal debridement (0.8%) and pulmonary embolus (0.6%). In addition, air leak at completion of open LVRS occurred in 54.3% of patients. Out of those patients with data on air leak after completion (n=339), 46% of patients had air leak for seven or more days. Out of 354 open LVRS patients who were not at high risk, 43.5% were in the intensive care unit (ICU) for one day or less, 15.3% for two days, 36.2% for 3 to 29 days, 2.3% for 30 days or more and 2.8% were dead within 30 days of LVRS. The reason for not including the full 359 patients is not reported. Out of 357 open LVRS patients who were not at high risk, 76.2% did not need mechanical ventilation after LVRS, 6.4% required one day, 6.2% for 2-14 days, 7.6% for 15-29 days, 0.8% for 30 days or more and 2.8% were dead within 30 days of LVRS. The reason for not including the full 359 patients is not reported. Only percentages were reported, not number of patients having complications. These results suggest a high rate of complications within 30 days after open LVRS with 58.4% of patients having a complication. Air leak is particularly high with just over a half of patients (54%) having air leak on completion of LVRS, followed by arrhythmia (21.3%) and pneumonia (20.1%). Three quarters of patients (76.2%) did not require mechanical ventilation after LVRS and 58.4% of patients were in ICU for two days or less. The importance of some of these complications to patients and to long term outcomes is not clear. These results are taken from a large group of patients having open LVRS (n=359) from a well conducted RCT and therefore provide good evidence of complications associated with open LVRS. However, the results reported for the duration of air leak, ICU stay and mechanical ventilation should be treated with caution as when calculating the percentages, it appears that data for patients who died within 30 days of surgery were excluded from the numerator but were included in the denominator which would make the results smaller than the true result, but should still reflect the true pattern of distribution for the lengths of complications.
Percentage hospitalised, living in a nursing or rehabilitation facility,	Naunheim et al (2006)	9	Direct	B	The percentage of patients hospitalised or living in a nursing or rehabilitation facility after surgery is an important indicator of independent living. The ability to live independently is an important component of QoL. Naunheim et al (2006) reported that 28.1%, 14.3%, 6.7%, and 3.3% of LVRS patients were hospitalised or living in a

Use of open lung volume reduction surgery vs maximal medical therapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
or unavailable for interview but not known to be dead					nursing or rehabilitation facility (or unavailable for interview but not known to be dead) at 1, 2, 4 and 8 months, respectively compared to 2.2%, 3.3%, 3.2% and 3.7% of control patients. These represented statistically significant differences between the groups at 1 to 4 months, but not at 8 months where only a 0.4% difference was observed. There is evidence to suggest that patients are more likely to be hospitalised or living in a nursing or rehabilitation facility up to four months after surgery, but no significant difference was seen longer-term at eight months between LVRS and medical management. These results are based on a well-conducted RCT with a large sample size (1,218) and therefore provide good evidence of a reduction in independence up to eight months after surgery. However only results up to eight months are provided so long-term effects on independence are not known. Furthermore, 30% of the LVRS group had VATS rather than open surgery which may have affected the results.
Hospital admissions, n	Miller et al (2005)	8	Direct	B	This is a measure of the number of LVRS patients readmitted into hospital after surgery and the number of control patients admitted into hospital during the trial period. Over a six-month period, Miller et al (2005) reported that 18/30 (60%) LVRS patients had 27 readmissions in the CLVR trial and 3/24 (12.5%) LVRS patients had three readmissions in the OBEST trial. In the control groups, 14/28 (50%) of control patients had 38 hospitalisations in the CLVR trial and 1/11 (9%) control patients in the OBEST trial. No confidence intervals or p-values were reported so it is not clear whether there was a significant difference in hospital admissions between the groups. In addition, no details on reason for admission were given. Given the relatively small numbers and lack of p-values or confidence intervals it is not possible to say whether LVRS is associated with an increase in hospital admissions compared to medical care or not. These results are based on a meta-analysis of 2 RCTS with a relatively small pooled sample size (n=93) and short follow-up of six months and hence there is likely to be a wide range of uncertainty around the observed difference.
Length of hospital stay, days	Miller et al (2005)	8	Direct	B	Length of hospital stay after surgery is an important indicator of the length of recovery after LVRS and use of hospital resources. It is also important as it will impact on a patient's QoL. Miller et al (2005) reported that the median length of hospital stay after surgery was 22 days (range 4 to 161 days) in the CLVR trial and 12 days (range 4 to 57) in the OBEST trial. The results show that patients tend to have relatively long stays in hospital after surgery of around 2-3 weeks. These results are based on a meta-analysis of two RCTS with a relatively small pooled sample size (n=93) and hence there is a wide range of lengths of hospital stay observed. In addition, the difference in median length of stay between the two trials suggests that it may vary markedly between hospitals or healthcare systems.

Use of open lung volume reduction surgery vs maximal medical therapy					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Cost per QALY	Ramsey et al (2007)	9	Direct	A	Cost effectiveness is measured as the cost of each additional quality adjusted life year (QALY) gained by the treatment (incremental cost effectiveness ratio or ICER). It is the ratio of the extra cost of LVRS (including follow-up and treatment of adverse events) above the cost for those having maximal medical therapy, to the additional QALYs gained due to surgery. Ramsey et al (2007), reported that the cost-effectiveness of LVRS vs medical therapy was found to be $140,000 per QALY gained (95% CI 40,155 to 239,359) at five years, and was projected to be $54,000 per QALY gained (confidence intervals not reported) at ten years. The cost-effectiveness of LVRS in patients with upper-lobe predominant emphysema and low exercise capacity at baseline (patient sub-group with greatest benefits) was $77,000 per QALY gained at five years and was projected to be $48,000 per QALY gained at ten years (confidence intervals not reported). The results show that the costs associated with LVRS are high and the cost-effectiveness is low. These results are based on a well conducted large RCT with long follow-up (up to five years). However, large uncertainty remains around the 10-year cost per QALYs as they are based on estimates of survival and QoL taken from data up to five years. In addition, the sub-group results are based on small numbers so will also have wide confidence intervals. Furthermore, the costs are from a US perspective and are over ten years old so may not be applicable to today's patients or to the UK NHS. The costs included medical goods and services, time spent in treatment, transportation to and from health-care facilities and time spent by family and friends caring for the patient, and some of these would not usually be included in cost-effectiveness studies carried out for the UK NHS.
	Miller et al (2006)	8			

9 Literature Search Terms

Search strategy *Indicate all terms used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroup s that need to be considered?	People with symptomatic **pulmonary emphysema** with demonstrable **hyperinflation** persisting after pulmonary rehabilitation. [Supporting information: • Clinical markers might include the following: FEV1 20-40% predicted, RV:TLC> 60 (hyperinflation), DLCO >20% predicted, pCO2 <7KPa, no evidence of pulmonary hypertension, RV >180%. • Subgroups with **heterogeneous emphysema** and with and without **collateral ventilation** should be considered.]
I – Intervention Which intervention, treatment or approach should be used?	Open lung volume reduction surgery
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Maximal medical therapy Lung volume reduction surgery using endobronchial valves
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	**Any including:** **Clinical effectiveness** **Cost effectiveness** **Critical to decision-making:** Improvement in health related quality of life: absolute reductions/improvements and percentage change mean difference (SF 36, SGRQ) Improvement in respiratory physiology: absolute and percentage change mean difference (increase in FEV1 and reduction in RV,) Survival rates at 30 days, 90 days, one year and five year **Important to decision-making:** Post-operative complications, including readmission with procedural complication Reduction in readmission rate for COPD exacerbation or other COPD related admission Improvement in MRC Dyspnoea scale Improvement in exercise capacity: absolute increase and increase percentage mean difference in 6 min walk test or shuttle walk test
Assumptions / limits applied to search	
Inclusion criteria: English language papers in peer reviewed journals from 2002 to date. Include case series where n>50 Exclusion criteria: limited case series n <50, case reports. Patients with coexisting malignancy, pulmonary fibrosis or pulmonary hypertension.	

10 Search Strategy

Embase: search date 15th of January 2018

# ▲	Searches
1	*chronic obstructive lung disease/ or exp lung emphysema/
2	((sever* or serious* or advanced) adj5 (emphysema or copd or chronic obstructive pulmonary disease or chronic obstructive lung disease)).ti,ab.
3	(emphysema or copd or chronic obstructive pulmonary disease or chronic obstructive lung disease).ti.
4	1 or 2 or 3
5	((lung or pulmonary) adj5 volume reduc*).ti,ab.
6	((lung volume or pulmonary volume) adj5 reduc*).ti,ab.
7	lvr.ti,ab.
8	5 or 6 or 7
9	lung surgery/
10	((open adj3 surg*) or thoracotom* or sternotom*).ti,ab.
11	((lung or pulmonary) adj3 surg*).ti,ab.
12	(reduc* adj3 surg*).ti,ab.
13	9 or 10 or 11 or 12
14	4 and 8 and 13
15	conference*.pt.
16	14 not 15
17	limit 16 to (english language and yr="2002 -Current")

11 Evidence Selection

- Total number of publications reviewed: 75
- Total number of publications considered potentially relevant: 47
- Total number of publications selected for inclusion in this briefing: 7

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